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Serine 199

L19 ANSWER 4 OF 47 MEDLINE
AN 2000167013 MEDLINE
DN 20167013
TI Distribution of **tau** protein kinase I/glycogen synthase
kinase-3beta, phosphatases 2A and 2B, and phosphorylated **tau** in
the developing rat brain.
AU Takahashi M; Tomizawa K; Ishiguro K
CS Project 8, Mitsubishi Kasei Institute of Life Sciences, 11 Minamiooya,
Machida-shi, Tokyo, Japan.. mlib@libra.ls.m-kagaku.co.jp
SO BRAIN RESEARCH, (2000 Feb 29) 857 (1-2) 193-206.
Journal code: B5L. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200007
EW 20000701
TI Distribution of **tau** protein kinase I/glycogen synthase
kinase-3beta, phosphatases 2A and 2B, and phosphorylated **tau** in
the developing rat brain.
AB When trying to elucidate the role played by **tau** protein kinase
I/glycogen synthase kinase-3beta (TPKI/GSK-3beta) in **tau**
phosphorylation, it is important to consider the balance that exists
between the various kinases and phosphatases that are involved in. . .
white matter were immunoreactive. Later, after 5 weeks, the
immunoreactivity became more restricted to the gray matter. The staining
of **tau** phosphorylated at Ser 119, Ser 396,
and Ser 413 followed mostly the pattern of the kinase
distribution throughout all stages of development. These data, therefore,
confirm that TPKI/GSK-3beta is. . .
CT Check Tags: Animal; Comparative Study
***tau Proteins: ME, metabolism**
Blotting, Western
Brain: CY, cytology
*Brain: GD, growth & development
*Brain: ME, metabolism
*Ca(2+)-Calmodulin Dependent Protein Kinase:. . . cytology
Neocortex: GD, growth & development
Neocortex: ME, metabolism
Neurons: CY, cytology
Neurons: ME, metabolism
*Phosphoprotein Phosphatase: ME, metabolism
Phosphorylation
***Protein-Serine-Threonine Kinases: ME, metabolism**
Rats
Rats, Wistar
CN EC 2.7.1.- (myelin basic protein kinase); EC 2.7.1.135 (**tau**
-protein kinase); EC 2.7.1.136 (**Protein-Serine-Threonine Kinases**);
EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 3.1.3.-
(Calcineurin); EC 3.1.3.16 (Phosphoprotein Phosphatase); 0 (**tau**
Proteins)

L19 ANSWER 5 OF 47 MEDLINE
 AN 2000143550 MEDLINE
 DN 20143550
 TI Conformation of paired helical filaments blocks dephosphorylation of epitopes shared with fetal tau except Ser199/202 and Ser202/Thr205.
 AU Gordon-Krajcer W; Yang L; Ksienk-Reding H
 CS Department of Pathology, Rm. F-538, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY, USA.
 NC NS35254 (NINDS)
 SO BRAIN RESEARCH, (2000 Feb 21) 856 (1-2) 163-75.
 Journal code: B5L. ISSN: 0006-8993.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200007
 EW 20000702
 TI Conformation of paired helical filaments blocks dephosphorylation of epitopes shared with fetal tau except Ser199/202 and Ser202/Thr205.
 AB . . . studied in vitro dephosphorylation of intact PHFs, PHFs with filamentous structure abolished by formic acid treatment (PHF(FA)) and fetal human tau protein. Samples were treated with alkaline phosphatase for up to 24 h at 37 degrees C and then immunoblotted with eight well characterized tau antibodies, that recognize two phosphorylation-insensitive sites and six phosphorylation-sensitive epitopes at Thr181, Ser199/202, Ser202/Thr205, Thr231, Ser262/356 and Ser396/404. Intact PHFs were effectively dephosphorylated only at the two N-terminal epitopes Ser199/202 and Ser202/Thr205, with little change in electrophoretic mobility. In contrast, PHF(FA) were dephosphorylated at all epitopes, with particular effectiveness at those in the C-terminus and with significant increase in electrophoretic mobility. The fetal tau epitopes were effectively dephosphorylated except at Thr181 and Thr231 with marked increase in mobility. The extent of dephosphorylation of PHF(FA) was equal or more effective than in fetal tau, except for Thr181 that was minimally dephosphorylated in both proteins. The results indicate that intact PHFs, but not PHF(FA), and fetal tau display differential dephosphorylation of the C-terminal epitopes. The results confirm that the filamentous conformation may significantly contribute to hyperphosphorylation of PHFs in the C-terminus. The filamentous conformation, however, does not limit access to two N-terminal epitopes Ser199/202 and Ser202/Thr205. The access to these sites in AD may be limited by other factors, e.g., inhibition of phosphatase binding.
 CT Check Tags: Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
 *tau Proteins: CH, chemistry
 *tau Proteins: ME, metabolism
 Aged
 Aged, 80 and over
 Alkaline Phosphatase
 *Alzheimer Disease: PA, pathology
 Amino Acid Sequence
 *Brain: PA, pathology
 . . . metabolism
 Fetus
 Formic Acids
 Kinetics

Middle Age

Neuropil Threads: ME, medial septum

*Neuropil Threads: PA, paraventricular

*Neuropil Threads: UL, ultrastructure

Phosphorylation

Serine

Threonine

RN **56-45-1 (Serine)**; 64-18-6 (aspartic acid); 72-19-5 (Threonine)

CN EC 3.1.3.1 (Alkaline Phosphatase); 0 (**tau** Proteins); 0
(Epit

L19 ANSWER 11 OF 47 MEDLINE
 AN 1998234266 MEDLINE
 DN 98234266
 TI Characterization of **tau** phosphorylation in glycogen synthase kinase-3beta and cyclin dependent kinase-5 activator (p23) transfected cells.
 AU Michel G; Mercken M; Murayama M; Noguchi K; Ishiguro K; Imahori K; Takashima A
 CS Mitsubishi Kasei Institute of Life Sciences, 11 Minamiooya, Machida-shi, Tokyo 194, Japan.
 SO BIOCHIMICA ET BIOPHYSICA ACTA, (1998 Apr 10) 1380 (2) 177-82.
 Journal code: AOW. ISSN: 0006-3002.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199807
 EW 19980704
 TI Characterization of **tau** phosphorylation in glycogen synthase kinase-3beta and cyclin dependent kinase-5 activator (p23) transfected cells.
 AB One of the histopathological markers in Alzheimer's disease is the accumulation of hyperphosphorylated **tau** in neurons called neurofibrillary tangles (NFT) composing paired helical filaments (PHF). Combined **tau** protein kinase II (TPK II), which consists of CDK5 and its activator (p23), and glycogen synthase kinase-3beta (GSK-3beta) phosphorylate **tau** to the PHF-form in vitro. To investigate **tau** phosphorylation by these kinases in intact cells, the phosphorylation sites were examined in detail using well-characterized phosphorylation-dependent anti-**tau** antibodies after overexpressing the kinases in COS-7 cells with a human **tau** isoform. The overexpression of **tau** in COS-7 cells showed extensive phosphorylation at Ser-202 and Ser-404. The p23 overexpression induced a mobility shift of **tau**, but most of the phosphorylation sites overlapped the endogenous phosphorylation sites.
 GSK-3beta transfection showed the phosphorylation at Ser-199, Thr-231, Ser-396, and Ser-413. Triplicated transfection resulted in phosphorylation of **tau** at 8 observed sites (Ser-199, Ser-202, Thr-205, Thr-231, Ser-235, Ser-396, Ser-404, and Ser-413).
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 CT Check Tags: Animal
 tau Proteins: GE, genetics
 ***tau** Proteins: ME, metabolism
 Antibodies: IM, immunology
 Antibodies: ME, metabolism
 Antibody Specificity
 Binding Sites: IM, immunology
 Ca(2+)-Calmodulin Dependent Protein Kinase: GE, . . . Kinase: ME, metabolism
 Cyclin-Dependent Kinases: GE, genetics
 *Cyclin-Dependent Kinases: ME, metabolism
 COS Cells
 Enzyme Activation
 Gene Expression: GE, genetics
 Phosphorylation
 Serine: IM, immunology
 Serine: ME, metabolism

Transfection

RN

56-45-1 (Serine)

CN

EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); 0 (**tau**
Proteins); 0 (Antibodies); 0 (Cyclin-Dependent Kinases)

L19 ANSWER 12 OF 47 MEDLINE

AN 1998185487 MEDLINE

DN 98185487

TI Selective expression of Ser 199/202 phosphorylated
tau in a case of frontotemporal dementia.

AU Takamatsu J; Kondo A; Ikegami K; Kimura T; Fujii H; Mitsuyama Y;
Hashizume

Y

CS Division of Clinical Research, Kikuchi National Hospital, Kumamoto,
Japan.

SO DEMENTIA AND GERIATRIC COGNITIVE DISORDERS, (1998 Mar-Apr) 9 (2) 82-9.
Journal code: CTT. ISSN: 1420-8008.

CY Switzerland

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199807

EW 19980702

TI Selective expression of Ser 199/202 phosphorylated
tau in a case of frontotemporal dementia.

AB . . . with dementia (MNDD) has not yet been established, and they are
included in one spectrum. Antibodies against paired helical filament
tau protein demonstrated immunopositive cytoskeletal structures
within the neurons as well as the glial cells in the brain of the present
case. They were selectively stained with **tau 199/**
202 but not **tau 396**, which were provided newly
to recognize phosphorylation at Ser 199/202 or Ser
396 in **tau**, respectively. We investigated **tau**
pathology in the present case in comparison to 8 cases with PD that were
clinicopathologically confirmed. Neither **tau 199/**
202 nor **tau 396** stained the CNS structures in
PD cases with few PBs, while both stained evidently those as well as PBs
in. . . PBs; so that the present case could be distinguished from PD

on

the basis of the immunoreactivity to site-specific phosphorylated
tau. Our result suggests that FTD, especially familial FLD type
might involve unique **tau** pathology, no matter whether FLD is a
distinct entity from PD, or a variant form in the wide FTD spectrum. .

CT Check Tags: Case Report; Comparative Study; Human; Male

tau Proteins: AN, analysis

***tau Proteins: ME, metabolism**

Adult

Aged

Aged, 80 and over

Dementia: DI, diagnosis

Dementia: GE, genetics

***Dementia: ME, metabolism**

Frontal Lobe: . . . CH, chemistry

Hippocampus: PA, pathology

Inclusion Bodies: PA, pathology

Magnetic Resonance Imaging

Middle Age

Neurofibrillary Tangles: PA, pathology

Pedigree

Phosphorylation

Serine: ME, metabolism

Temporal Lobe: CH, chemistry

***Temporal Lobe: PA, pathology**

RN 56-45-1 (Serine)

L19 ANSWER 15 OF 47 MEDLINE
 AN 97345393 MEDLINE
 DN 97345393
 TI Immunohistochemical examination of phosphorylated **tau** in
 granulovacuolar degeneration granules.
 AU Ikegami K; Kimura T; Katsuragi S; Ono T; Yamamoto H; Miyamoto E; Miyakawa
 T
 CS Division of Clinical Research, National Kikuchi Hospital, Kumamoto,
 Japan.
 SO PSYCHIATRY AND CLINICAL NEUROSCIENCES, (1996 Jun) 50 (3) 137-40.
 Journal code: CFS. ISSN: 1323-1316.
 CY Australia
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199710
 TI Immunohistochemical examination of phosphorylated **tau** in
 granulovacuolar degeneration granules.
 AB . . . GVD is formed through lysosomal autophagy of intraneuronal
 substances. We recently demonstrated that in non-demented cases NFT was
 phosphorylated at **serines 199, 202 and**
422 in paired helical filament (PHF)-**tau** more than in
serine 396, while NFT in AD cases was similarly
 phosphorylated at these four sites in **tau**. In this study, we
 demonstrated immunohistochemically a similar phosphorylation state of
tau in GVD granules to that in NFT in both non-demented cases and
 AD patients by using a mouse monoclonal anti-**tau** antibody and
 three phosphorylation site-specific antibodies for PHF-**tau**,
 indicating that GVD granules and NFT are composed of similar
 phosphorylated-**tau**. However, we could not detect PHF structures
 within any GVD using electronmicroscopy, indicating that PHF itself is
 not phagocytized by lysosomes during GVD formation. Therefore, the source of
 GVD granules might be phosphorylated pre-PHF-**tau**.
 CT Check Tags: Case Report; Human
 ***tau Proteins: AN, analysis**
 Aged
 Alzheimer Disease: ME, metabolism
 *Alzheimer Disease: PA, pathology
 Antibodies, Monoclonal
 *Hippocampus: CH, chemistry
 *Hippocampus: PA, pathology
 . . .
 CN 0 (**tau** Proteins); 0 (Antibodies, Monoclonal)

L19 ANSWER 16 OF 47 MEDLINE
 AN 97270620 MEDLINE
 DN 97270620
 TI Phosphorylation of **tau** by glycogen synthase kinase 3beta affects the ability of **tau** to promote microtubule self-assembly.
 AU Utton M A; Vandecandelaere A; Wagner U; Reynolds C H; Gibb G M; Miller C C; Bayley P M; Anderton B H
 CS Department of Neuroscience, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, U.K.
 SO BIOCHEMICAL JOURNAL, (1997 May 1) 323 (Pt 3) 741-7.
 Journal code: 9YO. ISSN: 0264-6021.
 CY ENGLAND: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199709
 TI Phosphorylation of **tau** by glycogen synthase kinase 3beta affects the ability of **tau** to promote microtubule self-assembly.
 AB To study the effects of phosphorylation by glycogen synthase kinase-3beta (GSK-3beta) on the ability of the microtubule-associated protein **tau** to promote microtubule self-assembly, **tau** isoform 1 (foetal **tau**) and three mutant forms of this **tau** isoform were investigated. The three mutant forms of **tau** had the following **serine** residues, known to be phosphorylated by GSK-3, replaced with alanine residues so as to preclude their phosphorylation: (1) Ser-199 and Ser-202 (Ser-199/202 -->Ala), (2) Ser-235 (Ser-235-->Ala) and (3) Ser-396 and Ser-404 (Ser-396/404-->Ala). Wild-type **tau** and the mutant forms of **tau** were phosphorylated with GSK-3beta, and their ability to promote microtubule self-assembly was compared with the corresponding non-phosphorylated **tau** species. In the non-phosphorylated form, wild-type **tau** and all of the mutants affected the mean microtubule length and number concentrations of assembled microtubules in a manner consistent with enhanced microtubule nucleation. Phosphorylation of these **tau** species with GSK-3beta consistently reduced the ability of a given **tau** species to promote microtubule self-assembly, although the affinity of the **tau** for the microtubules was not greatly affected by phosphorylation since the **tau** species remained largely associated with the microtubules. This suggests that the regulation of microtubule assembly can be controlled by phosphorylation of **tau** at sites accessible to GSK-3beta by a mechanism that does not necessarily involve the dissociation of **tau** from the microtubules.
 CT Check Tags: Animal; Support, Non-U.S. Gov't
 ***tau** Proteins: ME, metabolism
 Alzheimer Disease: ME, metabolism
 Ca(2+)-Calmodulin Dependent Protein Kinase: GE, genetics
 *Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
 Escherichia. . .
 CN EC 2.7.1.- (myelin basic protein kinase); EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); 0 (**tau** Proteins); 0 (Recombinant Fusion

L19 ANSWER 24 OF 47 MEDLINE
 AN 96432851 MEDLINE
 DN 96432851
 TI Sequential changes of **tau**-site-specific phosphorylation during development of paired helical filaments.
 AU Kimura T; Ono T; Takamatsu J; Yamamoto H; Ikegami K; Kondo A; Hasegawa M; Ihara Y; Miyamoto E; Miyakawa T
 CS Division of Clinical Research, National Kikuchi Hospital, Kumamoto, Japan.
 SO DEMENTIA, (1996 Jul-Aug) 7 (4) 177-81.
 Journal code: BUU. ISSN: 1013-7424.
 CY Switzerland
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199704
 TI Sequential changes of **tau**-site-specific phosphorylation during development of paired helical filaments.
 AB It has been reported that many **tau** sites in neurofibrillary tangles (NFT) are abnormally phosphorylated. We investigated the phosphorylation of **tau** in the hippocampus of nondemented patients and Alzheimer's disease patients by immunostaining with five site-specific antibodies against phosphorylated **tau**. In the pretangle stage, **tau** in neuropil threads was phosphorylated at **serines 199, 202 and 409**, numbered according to the longest human **tau** isoform, whereas **tau** in some neuronal soma was phosphorylated at **serines 199, 202, 409 and 422**. **Tau** at the stage of NFT was phosphorylated at **serine 396 and threonine 231** in addition to **serines 199, 202, 409 and 422**. In the advanced stage, **tau** in ghost tangles was phosphorylated mainly at **serine 396**. These results suggest that the phosphorylation of each site in **tau** differs among the maturing stages of neurofibrillary change and that abnormal phosphorylation of **tau** in the neuronal soma occurs at **199, 202, 409 and 422** earlier than at **threonine 231 and serine 396**.
 CT Check Tags: Human; Support, Non-U.S. Gov't
 ***tau Proteins: ME, metabolism**
 Adult
 Aged
 Aged, 80 and over
 *Alzheimer Disease: ME, metabolism
 Alzheimer Disease: PA, pathology
 *Cytoskeleton: ME, metabolism
 . . Immunohistochemistry
 Middle Age
 *Neurofibrillary Tangles: ME, metabolism
 Neurofibrillary Tangles: PA, pathology
 Phosphorylation
 Psychiatric Status Rating Scales
 Pyramidal Cells: PH, physiology
Serine: ME, metabolism
Threonine: ME, metabolism
 RN 56-45-1 (Serine); 72-19-5 (Threonine)
 CN 0 (**tau Proteins**)

L19 ANSWER 26 OF 47 MEDLINE
 AN 96303383 MEDLINE
 DN 96303383
 TI Neurodegenerative changes including altered **tau** phosphorylation
 and neurofilament immunoreactivity in mice transgenic for the
serine/threonine kinase Mos.
 AU James N D; Davis D R; Sindon J; Hanger D P; Brion J P; Miller C C;
 Rosenberg M P; Anderton B H; Propst F
 CS Ludwig Institute for Cancer Research, London, UK.
 SO NEUROBIOLOGY OF AGING, (1996 Mar-Apr) 17 (2) 235-41.
 Journal code: NX5. ISSN: 0197-4580.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199612
 TI Neurodegenerative changes including altered **tau** phosphorylation
 and neurofilament immunoreactivity in mice transgenic for the
serine/threonine kinase Mos.
 AB Transgenic mice expressing the oncogenic protein-**serine**
 /threonine kinase Mos at high levels in the brain display progressive
 neuronal degeneration and gliosis. Gliosis developed in parallel with
 the.
 . . postnatal transgene expression and led to a dramatic increase in
 the
 number of astrocytes positive for GFAP, vimentin, and possibly **tau**
 . Interestingly, vimentin is normally expressed only in immature or
 neoplastic astrocytes, but appears to be induced to high levels in
 Mos-transgenic, mature astrocytes. Mos can activate mitogen activated
 protein kinase (MAPK) and MAPK has been implicated in Alzheimer-type
tau phosphorylation. In the Mos-transgenic brain we found
 increased levels of phosphorylation at one epitope on **tau**
 containing **serines** 199 and 202 (numbering
 according to human **tau**), a pattern similar but not identical to
 that found in Alzheimer's disease. In addition, Mos-transgenic mice
 express a novel neurofilament-related. . .
 CT Check Tags: Animal; Female; Human; Male; Support, Non-U.S. Gov't
***tau Proteins: ME, metabolism**
 Brain Chemistry: GE, genetics
 Epitopes: GE, genetics
 Glial Fibrillary Acidic Protein: ME, metabolism
 Gliosis: PA, pathology
 Immunoblotting
 CN 0 (**tau** Proteins); 0 (Epitopes); 0 (Glial Fibrillary Acidic
 Protein); 0 (Neurofilament Proteins); 0 (Oncogene Proteins v-mos); 0
 (RNA,
 Messenger); 0 (Vimentin)

L19 ANSWER 31 OF 47 MEDLINE
 AN 95366974 MEDLINE
 DN 95366974
 TI The phosphorylation state of the microtubule-associated protein **tau** as affected by glutamate, colchicine and beta-amyloid in primary rat cortical neuronal cultures.
 AU Davis D R; Brion J P; Couck A M; Gallo J M; Hanger D P; Ladhani K; Lewis C; Miller C C; Rupniak T; Smith C; et al
 CS Department of Neuroscience, Institute of Psychiatry, London, UK.
 SO BIOCHEMICAL JOURNAL, (1995 Aug 1) 309 (Pt 3) 941-9.
 Journal code: 9YO. ISSN: 0264-6021.
 CY ENGLAND: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199511
 TI The phosphorylation state of the microtubule-associated protein **tau** as affected by glutamate, colchicine and beta-amyloid in primary rat cortical neuronal cultures.
 AB . . . of the excitatory amino acid glutamate, the microtubule destabilizing agent colchicine, and beta 25-35-amyloid peptide on the phosphorylation state of **tau** were studied in rat cortical neurons in primary culture. Using immunocytochemistry and Western-blot analysis, we demonstrated that a proportion of **tau** in these cultures is normally highly phosphorylated, but most of this **tau** fraction is dephosphorylated after treatment of the cultures with glutamate or colchicine, but not with beta-amyloid; the glutamate- and colchicine-induced changes in **tau** phosphorylation commenced before cell death, as assessed by release of lactate dehydrogenase. Dephosphorylation of **tau** was readily revealed by using the monoclonal antibodies **Tau.1** and AT8, which have phosphate-sensitive epitopes that both centre around **serine-199** and **-202** (numbering of the largest **tau** isoform). On Western blots and by immunocytochemistry, AT8 labelling strongly decreased after glutamate and colchicine treatments, whereas **Tau.1** staining was more intense. Neurofilament monoclonal antibodies, including RT97, 8D8, SMI31 and SMI310, all additionally known to recognize **tau** in a phosphorylation-dependent manner, also demonstrated that glutamate and colchicine treatments of the cultures induced a dephosphorylation of **tau**. We also showed immunocytochemically that there is an increase in **tau** immunoreactivity in neuronal perikarya in response to glutamate and colchicine treatment, and this occurs concomitantly with the dephosphorylation of **tau**. Treatment of the primary rat cortical neuronal cultures with beta 25-35-amyloid peptide, under conditions which induce neuronal degeneration, did not induce a change in **tau** phosphorylation, and failed to act synergistically with glutamate to produce an increase in dephosphorylation of **tau** over that produced by glutamate treatment alone. These findings demonstrate that glutamate and colchicine induce **tau** dephosphorylation, as opposed to increased **tau** phosphorylation, which would be more indicative of Alzheimer-type neurodegeneration.
 CT Check Tags: Animal; Support, Non-U.S. Gov't
 ***tau** Proteins: ME, metabolism
 *Amyloid beta-Protein: PD, pharmacology
 Cells, Cultured
 Cerebral Cortex: CY, cytology
 Cerebral Cortex: DE, drug effects
 Cerebral Cortex: . . .
 CN EC 3.1.3.16 (Phosphoprotein Phosphatase); 0 (**tau** Proteins); 0

L19 ANSWER 33 OF 47 MEDLINE

AN 95307471 MEDLINE

DN 95307471

TI Dephosphorylation of abnormal sites of **tau** factor by protein phosphatases and its implication for Alzheimer's disease.

AU Ono T; Yamamoto H; Tashima K; Nakashima H; Okumura E; Yamada K; Hisanaga S; Kishimoto T; Miyakawa T; Miyamoto E

CS Department of Pharmacology, Kumamoto University School of Medicine, Japan.

SO NEUROCHEMISTRY INTERNATIONAL, (1995 Mar) 26 (3) 205-15.

Journal code: BNU. ISSN: 0197-0186.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199509

TI Dephosphorylation of abnormal sites of **tau** factor by protein phosphatases and its implication for Alzheimer's disease.

AB The abnormally phosphorylated forms of **tau** factor are major constituents of neurofibrillary tangles in Alzheimer's disease brain. In order to investigate protein phosphatases which are related to dephosphorylation of abnormal phosphorylation sites, we examined the dephosphorylation of **tau** factor phosphorylated by three proline-directed type protein kinases. **Tau** factor phosphorylated by cdc2 kinase and **tau** protein kinase II was dephosphorylated by the holoenzyme of protein phosphatase 2A and calcineurin, while either

the

catalytic subunit of protein phosphatase 2A or protein phosphatase 2C could not catalyze the dephosphorylation. From the kinetic analysis, we concluded that **tau** factors phosphorylated by the protein kinases serve as good substrates for protein phosphatase 2A and calcineurin. On the other hand, **tau** factor phosphorylated by glycogen synthase kinase 3 alpha was dephosphorylated by the catalytic subunit of protein phosphatases 2A as well as the holoenzyme of protein phosphatase 2A and calcineurin. It has been reported that **serines 199, 202 and 396** according to the numbering of the longest human **tau** isoform are among the major abnormal phosphorylation sites of **tau** factor. We synthesized two phosphopeptides which contained phosphoserines **199** and **202** or phosphoserine **396** and prepared the polyclonal antibodies specific for the phosphopeptides. Using these antibodies, we confirmed that the holoenzyme of protein phosphatase 2A and calcineurin could dephosphorylate phosphoserines **199, 202 and 396** in **tau** factor. The catalytic subunit of protein phosphatase 2A could dephosphorylate phosphoserine **396** but not phosphoserines **199 and 202**. Neurofibrillary tangles in Alzheimer's disease brain were immunostained with both antibodies but the normal neurons in the normal aged brains. . . The results suggest that

protein

phosphatase 2A and calcineurin can be involved in the dephosphorylation

of

abnormal phosphorylation sites in **tau** factor and that the dephosphorylation of phosphoserine **396** is differently regulated from phosphoserines **199 and 202**.

CT . . .

Middle Age

Neurofibrillary Tangles: ME, metabolism

Peptide Mapping

Phosphopeptides: ME, metabolism

*Phosphoprotein Phosphatase: ME, metabolism

Phosphorylation
Protein p34cdc2: ME, metabolism
Protein-Serine-Threonine Kinases: ME, metabolism
Transcription Factors: CH, chemistry
*Transcription Factors: ME, metabolism
CN EC 2.7.1.- (myelin basic protein kinase); EC 2.7.10 (Protein-
Serine-Threonine Kinases); EC 2.7.10.- (**tau** protein
kinase II); EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); EC
3.1.3.16 (Phosphoprotein Phosphatase); 0 (**tau** factor); 0
(Microtubule-Associated Proteins); 0 (Phosphopeptides); 0 (Protein
p34cdc2); 0 (Transcription Factors)

L19 ANSWER 36 OF 47 MEDLINE
 AN 95198033 MEDLINE
 DN 95198033
 TI Involvement of **tau** protein kinase I in paired helical filament-like phosphorylation of the juvenile **tau** in rat brain.
 AU Takahashi M; Tomizawa K; Ishiguro K; Takamatsu M; Fujita S C; Imahori K
 CS Mitsubishi Kasei Institute of Life Sciences, Tokyo, Japan..
 SO JOURNAL OF NEUROCHEMISTRY, (1995 Apr) 64 (4) 1759-68.
 Journal code: JAV. ISSN: 0022-3042.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199506
 TI Involvement of **tau** protein kinase I in paired helical filament-like phosphorylation of the juvenile **tau** in rat brain.
 AB **tau** protein kinase I (TPKI) phosphorylates **tau** and forms paired helical filament epitopes in vitro. We studied temporal expression and histochemical distribution of **tau** phosphoserine epitopes at sites known to be phosphorylated by TPKI. Antibodies directed against phosphorylated Ser199 (anti-PS **199**) or phosphorylated Ser396 (C5 or anti-PS **396**) were used. TPKI is abundantly expressed in the young rat brain and the highly phosphorylated juvenile form of **tau** occurs in the same period. The activity peak of TPKI coincided with the high level of phosphorylation of Ser199 and Ser396 in juvenile **tau** at around postnatal day 8. By immunohistochemistry on the hippocampus and neocortex of 3-11-day-old rats, phosphorylated Ser396 was found in. . . immunoreactivities were also detected in the perikarya of pyramidal neurons. TPKI immunoreactivity had declined to a low level and phosphorylated **serine** immunoreactivities were undetectable in the sections of adult brain. These findings implicate
 TPKI in paired helical filament-like phosphorylation of juvenile form of **tau** in the developing brain.
 CT Check Tags: Animal; Support, Non-U.S. Gov't
 ***tau Proteins: ME, metabolism**
 Aging: ME, metabolism
 Animals, Newborn
 Antibodies, Monoclonal
 Brain: EM, embryology
 *Brain: ME, metabolism
 Immunoblotting
 Immunohistochemistry: MT, methods
 Phosphorylation
 Precipitin Tests
 ***Protein-Serine-Threonine Kinases: PH, physiology**
 Rats
 Tissue Distribution
 CN EC 2.7.1.135 (**tau**-protein kinase); EC 2.7.10 (Protein-Serine-Threonine Kinases); 0 (**tau** Proteins); 0 (Antibodies, Monoclonal)

L19 ANSWER 37 OF 47 MEDLINE
 AN 95180416 MEDLINE
 DN 95180416
 TI Abnormally phosphorylated **tau** in SY5Y human neuroblastoma cells.
 AU Tanaka T; Iqbal K; Trenkner E; Liu D J; Grundke-Iqbal I
 CS New York State Institute for Basic Research in Developmental
 Disabilities,
 Staten Island 10314.
 NC NS 18105 (NINDS)
 AG05892 (NIA)
 AG08076 (NIA)
 SO FEBS LETTERS, (1995 Feb 20) 360 (1) 5-9.
 Journal code: EUH. ISSN: 0014-5793.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199506
 TI Abnormally phosphorylated **tau** in SY5Y human neuroblastoma cells.
 AB In Alzheimer disease (AD) the microtubule associated protein (MAP)
tau is hyperphosphorylated at several sites. In the present study,
 like AD **tau**, **tau** in the human neuroblastoma SH-SY5Y
 was found to be hyperphosphorylated, at Ser-199/202,
 Thr-231, Ser-396 and Ser-404. However, in contrast to
 AD, the **tau** in SY5Y cells was not hyperphosphorylated at Ser-
 235 and there was only one **tau** isoform. Quantitative
 analysis revealed that approximately 80% of the SY5Y-**tau** was
 phosphorylated at Ser-199/202. The phosphorylated
tau was deposited in perikarya and processes of the cells whereas
 most of the unphosphorylated (at Ser-199/202)
tau was localized in the nucleus. **Tau** from the cell
 lysates did not bind to taxol-stabilized microtubules. In contrast, MAP1b
 and MAP2 from cell lysates bound to stabilized microtubules in vitro and
 were associated to the microtubule network in situ. Phosphorylation of
tau at high levels, its inactivity with microtubules and its
 accumulation in SY5Y cells provide for the first time a cell. . . .
 CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
***tau Proteins: ME, metabolism**
 Cytoplasm: ME, metabolism
 Microtubules: ME, metabolism
 Neuroblastoma: ME, metabolism
 Phosphorylation
 Protein Binding
Serine: ME, metabolism
 Tumor Cells, Cultured
 RN 56-45-1 (Serine)
 CN 0 (**tau** Proteins)

L19 ANSWER 39 OF 47 MEDLINE
 AN 94185781 MEDLINE
 DN 94185781
 TI Dephosphorylation of microtubule-associated protein **tau** by protein phosphatase-1 and -2C and its implication in Alzheimer disease.
 AU Gong C X; Grundke-Iqbal I; Damuni Z; Iqbal K
 CS New York State Institute for Basic Research in Developmental Disabilities,
 Staten Island, NY 10314.
 NC NS18105 (NINDS)
 AG05892 (NIA)
 AG08076 (NIA)
 +
 SO FEBS LETTERS, (1994 Mar 14) 341 (1) 94-8.
 Journal code: EUH. ISSN: 0014-5793.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199406
 TI Dephosphorylation of microtubule-associated protein **tau** by protein phosphatase-1 and -2C and its implication in Alzheimer disease.
 AB Microtubule-associated protein **tau** is abnormally hyperphosphorylated and forms the major protein subunit of paired helical filaments (PHF) in Alzheimer disease brains. The abnormally phosphorylated
 sites Ser-199, Ser-202, Ser-396 and Ser-404 but not Ser-46 and Ser-235 of Alzheimer **tau** were found to be dephosphorylated by protein phosphatase-1 and this dephosphorylation was activated by Mn²⁺. In contrast, protein phosphatase-2C did not dephosphorylate any of these sites. Both protein phosphatase-1 and -2C had high activities towards [32P]**tau** phosphorylated by cAMP-dependent protein kinase. These results suggest that both protein phosphatase-1 and -2C might be associated with normal phosphorylation state of **tau**, but only the former and not the latter phosphatase is involved in its abnormal phosphorylation in Alzheimer disease.
 CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
 ***tau** Proteins: ME, metabolism
 Aged
 Alzheimer Disease: EN, enzymology
 *Alzheimer Disease: ME, metabolism
 Cattle
 Cyclic AMP-Dependent Protein Kinases: ME, metabolism
 Middle Age
 *Phosphoprotein Phosphatase: ME, metabolism
 Phosphorylation
 Rabbits
 Serine: ME, metabolism
 RN 56-45-1 (Serine)
 CN EC 2.7.10.- (Cyclic AMP-Dependent Protein Kinases); EC 3.1.3.16 (Phosphoprotein Phosphatase); 0 (**tau** Proteins)

L19 ANSWER 40 OF 47 MEDLINE
 AN 94045667 MEDLINE
 DN 94045667
 TI Detection of **tau** proteins in normal and Alzheimer's disease
 cerebrospinal fluid with a sensitive sandwich enzyme-linked immunosorbent
 assay.
 AU Vandermeeren M; Mercken M; Vanmechelen E; Six J; van de Voorde A; Martin
 J
 J; Cras P
 CS Laboratory of Neurobiology, Born-Bunge Foundation, University of Antwerp,
 Wilrijk, Belgium.
 SO JOURNAL OF NEUROCHEMISTRY, (1993 Nov) 61 (5) 1828-34.
 Journal code: JAV. ISSN: 0022-3042.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199402
 TI Detection of **tau** proteins in normal and Alzheimer's disease
 cerebrospinal fluid with a sensitive sandwich enzyme-linked immunosorbent
 assay.
 AB . . . characterized by the abundant presence of neurofibrillary
 tangles
 in neurons. This study was designed to test whether the
 microtubule-associated protein **tau**, a major component of
 neurofibrillary tangles, could be detected in CSF. Additionally, we
 investigated whether CSF **tau** levels were abnormal in Alzheimer's
 disease as compared with a large group of control patients. We developed
 a
 sensitive sandwich enzyme-linked immunosorbent assay using AT120, a
 monoclonal antibody directed to human **tau**, as a capturing
 antibody. With this technique, the detection limit for **tau** was
 less than 5 pg/ml of CSF. Using AT8, which recognizes abnormally
 phosphorylated **serines 199-202** in
tau, the detection limit was below 20 pg/ml of CSF. However, with
 AT8, we found no immunoreactivity in CSF, suggesting that only a small
 fraction of CSF **tau** contains the abnormally phosphorylated AT8
 epitope. Our results indicate that CSF **tau** levels are
 significantly increased in Alzheimer's disease. Also, CSF **tau**
 levels in a large group of patients with a diversity of neurological
 diseases showed overlap with CSF **tau** levels in Alzheimer's
 disease.
 CT Check Tags: Comparative Study; Human
 ***tau Proteins: CF, cerebrospinal fluid**
 Adolescence
 Adult
 Age Factors
 Aged
 Aged, 80 and over
 *Alzheimer Disease: CF, cerebrospinal fluid
 Antibodies, Monoclonal
 . . .
 CN 0 (**tau** Proteins); 0 (Antibodies, Monoclonal)

IDS
 AK

L19 ANSWER 42 OF 47 MEDLINE
 AN 93288272 MEDLINE
 DN 93288272
 TI The phosphatase inhibitor okadaic acid induces a phosphorylated paired helical filament **tau** epitope in human LA-N-5 neuroblastoma cells.
 AU Vandermeeren M; Lubke U; Six J; Cras P
 CS Innogenetics, Ghent, Belgium.
 SO NEUROSCIENCE LETTERS, (1993 Apr 16) 153 (1) 57-60.
 Journal code: N7N. ISSN: 0304-3940.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199309
 TI The phosphatase inhibitor okadaic acid induces a phosphorylated paired helical filament **tau** epitope in human LA-N-5 neuroblastoma cells.
 AB . . . generation of a phosphorylated paired helical filament (PHF) epitope recognized by the monoclonal antibody AT8. This epitope consists of phosphorylated **serines 199** and/or **202** of the human microtubule associated protein **tau**. Theoretically, aside from abnormal kinase activity, inhibition of phosphatase activity could also be involved in the abnormal phosphorylation status of the microtubule associated protein **tau**. To investigate this, we incubated LA-N-5 neuroblastoma cells with okadaic acid, a specific inhibitor of phosphatase 2A. We found that. . . dependent and is reversible. Our findings suggest that phosphatase activity is important
 in the regulation of the phosphorylation state of **tau**. Phosphatases may act directly on **tau** or may influence the activity of mitogen activated protein kinase. Incubation of LA-N-5 neuroblastoma cells with okadaic acid provides a cellular model in which the generation of a well-defined PHF-**tau** epitope can be investigated.
 CT Check Tags: Human
 tau Proteins: IM, immunology
 ***tau Proteins: ME, metabolism**
 Epitopes
 *Ethers, Cyclic: PD, pharmacology
 Immunoblotting
 Neuroblastoma
 *Phosphoric Monoester Hydrolases: AI, antagonists & inhibitors
 Phosphorylation
 Tumor Cells, . . .
 CN EC 3.1.3 (Phosphoric Monoester Hydrolases); 0 (**tau Proteins**); 0 (Epitopes); 0 (Ethers, Cyclic)

L19 ANSWER 44 OF 47 MEDLINE
 AN 93204206 MEDLINE
 DN 93204206
 TI Application of synthetic phospho- and unphospho- peptides to identify phosphorylation sites in a subregion of the **tau** molecule, which is modified in Alzheimer's disease.
 AU Liu W K; Moore W T; Williams R T; Hall F L; Yen S H
 CS Department of Pathology, Albert Einstein College of Medicine, Bronx, New York 10461.
 NC AG01136 (NIA)
 AG04145 (NIA)
 SO JOURNAL OF NEUROSCIENCE RESEARCH, (1993 Feb 15) 34 (3) 371-6.
 Journal code: KAC. ISSN: 0360-4012.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199306
 TI Application of synthetic phospho- and unphospho- peptides to identify phosphorylation sites in a subregion of the **tau** molecule, which is modified in Alzheimer's disease.
 AB Phospho- and unphospho- peptides were used to define the essential sequence for a **tau** epitope, which is recognized by **Tau** -1 antibody and phosphorylated in Alzheimer's disease (AD). The epitope was mapped within the amino acid residues 192-199 of tau and was phosphorylated by the p34cdc2/p58cyclin A proline directed kinase (PDPK), but not by purified mitogen activated protein kinase (p42mapk). Addition of phosphate to the last **serine** of the epitope was the most effective in abolishing the reactivity of the epitope to **Tau** -1 antibody. Our results suggest that one and possibly more members of the PDPK family may play a role in the. . .
 CT Check Tags: Human; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
 tau Proteins: CH, chemistry
 tau Proteins: IM, immunology
 *tau Proteins: ME, metabolism
 *Alzheimer Disease: ME, metabolism
 Amino Acid Sequence
 DNA
 Enzyme-Linked Immunosorbent Assay
 Molecular Sequence Data
 *Neuropeptides: ME, metabolism
 CN EC 2.7.1.37 (Protein Kinases); EC 2.7.10.- (protein-proline kinase); 0 (tau Proteins); 0 (Neuropeptides); 0 (Phosphopeptides)

L19 ANSWER 46 OF 47 MEDLINE
 AN 92224898 MEDLINE
 DN 92224898
 TI The switch of **tau** protein to an Alzheimer-like state includes the phosphorylation of two **serine**-proline motifs upstream of the microtubule binding region.
 AU Biernat J; Mandelkow E M; Schroter C; Lichtenberg-Kraag B; Steiner B; Berling B; Meyer H; Mercken M; Vandermeeren A; Goedert M; et al
 CS Max-Planck-Unit for Structural Molecular Biology, Hamburg, FRG.
 SO EMBO JOURNAL, (1992 Apr) 11 (4) 1593-7.
 Journal code: EMB. ISSN: 0261-4189.
 CY ENGLAND: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199207
 TI The switch of **tau** protein to an Alzheimer-like state includes the phosphorylation of two **serine**-proline motifs upstream of the microtubule binding region.
 AB The paired helical filaments (PHFs) of Alzheimer's disease consist mainly of the microtubule-associated protein **tau**. PHF **tau** differs from normal human brain **tau** in that it has a higher Mr and a special state of phosphorylation. However, the protein kinase(s) involved, the phosphorylation sites on **tau** and the resulting conformational changes are only poorly understood. Here we show that a
 new
 monoclonal antibody, AT8, records the PHF-like state of **tau** in vitro, and we describe a kinase activity that turns normal **tau** into a PHF-like state. The epitope of AT8 is around residue 200, outside the region of internal repeats and requires the phosphorylation of **serines 199** and/or **202**. Both of these are followed by a proline, suggesting that the kinase activity belongs to the family of proline-directed kinases.. . .
 CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
 tau Proteins: GE, genetics
 ***tau Proteins: ME, metabolism**
 Alzheimer Disease: GE, genetics
 *Alzheimer Disease: ME, metabolism
 Amino Acid Sequence
 Binding Sites
 Brain: ME, metabolism
 Cattle
 . . . Sequence Data
 Peptide Fragments: IP, isolation & purification
 Phosphopeptides: IP, isolation & purification
 Phosphorylation
 Plasmids
 *Proline
 *Protein Kinases: ME, metabolism
 ***Serine**
 Swine
 RN 147-85-3 (Proline); **56-45-1 (Serine)**
 CN EC 2.7.1.37 (Protein Kinases); 0 (**tau Proteins**); 0 (Peptide Fragments); 0 (Phosphopeptides); 0 (Plasmids)

L4 ANSWER 1 OF 35 MEDLINE
 AN 2000069686 MEDLINE
 DN 20069686
 TI The neurite retraction induced by lysophosphatidic acid increases Alzheimer's disease-like Tau phosphorylation.
 AU Sayas C L; Moreno-Flores M T; Avila J; Wandosell F
 CS Centro de Biología Molecular "Severo Ochoa" Consejo Superior de Investigaciones Científicas-Universidad Autónoma de Madrid, Cantoblanco-Madrid 28049, Spain.
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Dec 24) 274 (52) 37046-52.
 Journal code: HIV. ISSN: 0021-9258.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 200003
 EW 20000303
 AB . . . demonstrate an increase in site-specific Alzheimer's disease-like Tau phosphorylation during LPA-induced neurite retraction in differentiated SY-SH5Y human neuroblastoma cells. The **phosphorylation** state of **Tau** was inferred from its **immunoreactivity** with **antibodies** that recognize **phosphorylation**-sensitive epitopes. The effects of specific kinase inhibitors indicate that this phosphorylation is mediated by glycogen synthase kinase-3 (GSK-3). In support. . .

=> d bib kwic 2-

YOU HAVE REQUESTED DATA FROM 34 ANSWERS - CONTINUE? Y/(N):y

L4 ANSWER 2 OF 35 MEDLINE
 AN 1999419285 MEDLINE
 DN 99419285
 TI Interaction of aluminum with PHFtau in Alzheimer's disease neurofibrillary degeneration evidenced by desferrioxamine-assisted chelating autoclave method.
 AU Murayama H; Shin R W; Higuchi J; Shibuya S; Muramoto T; Kitamoto T
 CS Department of Neurological Science, Tohoku University School of Medicine Sendai City Hospital, Sendai, Japan.
 SO AMERICAN JOURNAL OF PATHOLOGY, (1999 Sep) 155 (3) 877-85.
 Journal code: 3RS. ISSN: 0002-9440.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
 EM 199912
 EW 19991202
 AB . . . for Al attenuated the positive fluorescence of neurofibrillary tangles, indicating Al removal from them. This method, applied for immunostaining with **phosphorylation**-dependent anti-**tau antibodies**, significantly enhanced the PHFtau **immunoreactivity** of the NFD. These results suggest that each of the phosphorylated epitopes in PHFtau are partially masked by Al binding..

L4 ANSWER 3 OF 35 MEDLINE
 AN 1999304720 MEDLINE
 DN 99304720
 TI Immunohistochemical and ultrastructural characterization of neuritic clusters around ghost tangles in the hippocampal formation in progressive supranuclear palsy brains.
 AU Arima K; Nakamura M; Sunohara N; Nishio T; Ogawa M; Hirai S; Kawai M; Ikeda K
 CS Department of Ultrastructure and Histochemistry, Tokyo Institute of Psychiatry, Japan.. arima@prit.go.jp
 SO ACTA NEUROPATHOLOGICA, (1999 Jun) 97 (6) 565-76.
 Journal code: 1CE. ISSN: 0001-6322.
 CY GERMANY: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200003
 EW 20000304
 AB . . . between loosened fascicles of GTs or along their outer rims. There were several subsets of neurites that were argyrophilic or **immunoreactive** against **antibodies** to either **phosphorylated tau** protein, **phosphorylated** neurofilaments, ubiquitin, or synaptophysin. On EM, TANCs consisted of numerous axon terminals of varying size, which were filled with flocculate. . .

L4 ANSWER 4 OF 35 MEDLINE
 AN 1999113978 MEDLINE
 DN 99113978
 TI Transgenic expression of the shortest human tau affects its compartmentalization and its phosphorylation as in the pretangle stage of Alzheimer's disease [see comments].
 CM Comment in: Am J Pathol 1999 Jan;154(1):1-6
 AU Brion J P; Tremp G; Octave J N
 CS Laboratory of Pathology and Electron Microscopy, Universite Libre de Bruxelles, Brussels, Belgium.
 SO AMERICAN JOURNAL OF PATHOLOGY, (1999 Jan) 154 (1) 255-70.
 Journal code: 3RS. ISSN: 0002-9440.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
 EM 199904
 EW 19990402
 AB . . . transgenic tau remained abundant in cell bodies and dendrites of a subset of neurons in the adult. This somatodendritic transgenic **tau** was **immunoreactive** with **antibodies** to **tau phosphorylated** on Thr181 and Thr231 and with the conformation-dependent Alz50 **antibody**. A few astrocytes expressing the transgenic **tau** were strongly **immunoreactive** with **antibodies** to additional **tau phosphorylation** sites, ie, at Ser262/ 356 and Ser396/404. All of these phosphorylation sites have been identified in paired helical filaments-tau proteins.. . .

L4 ANSWER 5 OF 35 MEDLINE
 AN 1999007104 MEDLINE
 DN 99007104
 TI Ballooned neurons expressing alphaB-crystallin as a constant feature of the amygdala in argyrophilic grain disease.
 AU Tolnay M; Probst A
 CS Institute of Pathology, Division of Neuropathology, Basel University, Switzerland.. probstal@ubaclu.unibas.ch
 SO NEUROSCIENCE LETTERS, (1998 May 1) 246 (3) 165-8.
 Journal code: N7N. ISSN: 0304-3940.

CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
AB . . . with AgD BNs were randomly dispersed throughout the amygdala and were associated with various numbers of argyrophilic grains (ArGs) and **tau immunoreactive** non-ballooned neurons. BNs were strongly labelled with **antibodies** against alphaB-crystallin, **phosphorylated tau** (AT8, PHF-1) and **phosphorylated** neurofilament (SMI-31). In contrast AT8-**immunoreactive** non-ballooned neurons and ArGs remained consistently unstained with the alphaB-crystallin antibody. Our findings suggest that in AgD two different pathological. . .

L4 ANSWER 6 OF 35 MEDLINE
AN 1998361389 MEDLINE
DN 98361389
TI Apolipoprotein E and Tau phosphorylation in human neuroblastoma cells.
AU Caillet-Boudin M L; Dupont-Wallois L; Soulie C; Delacourte A
CS INSERM U422, Pl. Verdun, Lille, France.. caillet@biserte.inserm.lille.fr
SO NEUROSCIENCE LETTERS, (1998 Jul 3) 250 (2) 83-6.
Journal code: N7N. ISSN: 0304-3940.

CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199907
EW 19990703
AB . . . this cellular model makes it possible to study the differential influence, if any, of apo E3 and E4 on Tau **phosphorylation**. Using a large panel of Tau **phosphorylation**-dependent **antibodies**, we were not able to detect a significant difference in **Tau immunoreactivity** linked to the different apo E genotypes, even when the hyperphosphorylation of Tau proteins was induced by treating cells with. . .

L4 ANSWER 7 OF 35 MEDLINE
AN 1998328556 MEDLINE
DN 98328556
TI Emergence of immunoreactivities for phosphorylated tau and amyloid-beta protein in chronic stage of fluid percussion injury in rat brain.
AU Hoshino S; Tamaoka A; Takahashi M; Kobayashi S; Furukawa T; Oaki Y; Mori O; Matsuno S; Shoji S; Inomata M; Teramoto A
CS Department of Neurosurgery, Nippon Medical School, Chiba Hokusoh Hospital, Chiba, Japan.
SO NEUROREPORT, (1998 Jun 1) 9 (8) 1879-83.
Journal code: A6M. ISSN: 0959-4965.

CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199810
EW 19981003
AB . . . brain injury (3.6-4.8 atm) in rats. Six months after injury, numerous normal-looking neurons in the telencephalon and brain stem were **immunoreactive** with either **antibody** to **phosphorylated tau** or with four **antibodies** to beta-amyloid protein. Neuronal counts in the cortices were gradually decreased after injury, up to 42% loss at 6 months. . .

L4 ANSWER 8 OF 35 MEDLINE
AN 1998270047 MEDLINE
DN 98270047
TI Developmental regulation and PKC dependence of Alzheimer's-type tau

phosphorylations in cultured fetal rat hippocampal neurons.

AU Combs C K; Coleman P D; O'Banion M K
 CS Department of Neurobiology and Anatomy, University of Rochester School of
 Medicine and Dentistry, NY 14642, USA.
 NC AG09016 (NIA)
 R01 AG1121 (NIA)
 T32 AG107 (NIA)
 +
 SO BRAIN RESEARCH. DEVELOPMENTAL BRAIN RESEARCH, (1998 Apr 17) 107 (1)
 143-58.
 Journal code: DBR. ISSN: 0165-3806.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199810
 EW 19981001
 AB . . . staining and Western blots. Tau was heavily phosphorylated at
 the
 Tau 1 epitope only in older cultures. The populations of **tau**
 recognized by the two **antibodies** also exhibited different
 solubilities, suggesting different microtubule **binding**
 behaviors: **tau phosphorylated** at PHF-1 was retained in
 axons following solubilization whereas Tau 1 immunoreactive tau was not
 retained in any cell compartment.. . .

L4 ANSWER 9 OF 35 MEDLINE
 AN 97474239 MEDLINE
 DN 97474239
 TI Beta-amyloid and ionophore A23187 evoke tau hyperphosphorylation by
 distinct intracellular pathways: differential involvement of the
 calpain/protein kinase C system.
 AU Shea T B; Prabhakar S; Ekinici F J
 CS Center for Cellular Neurobiology and Neurodegeneration Research,
 Department of Biological Sciences, University of Massachusetts at Lowell,
 01854, USA.. SheaTH@Woods.uml.edu
 NC AG10916 (NIA)
 SO JOURNAL OF NEUROSCIENCE RESEARCH, (1997 Sep 15) 49 (6) 759-68.
 Journal code: KAC. ISSN: 0360-4012.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199801
 EW 19980104
 AB . . . with paired helical filaments (PHFs) and towards an antibody
 (5E2) that recognized a phosphate-independent tau epitope. However, only
 ionophore increased **immunoreactivity** with an additional
 phosphate-dependent **antibody** (AT-8) that recognized an epitope
 of **tau** when **phosphorylated**, and induced a
 corresponding decrease in **immunoreactivity** towards an additional
antibody (Tau-1) that recognizes the same site when that
 site is not phosphorylated. Moreover, the ionophore-mediated increase in
 PHF-1 was blocked by. . .

L4 ANSWER 10 OF 35 MEDLINE
 AN 97465564 MEDLINE
 DN 97465564
 TI Tau released from paired helical filaments with formic acid or guanidine
 is susceptible to calpain-mediated proteolysis.
 AU Yang L S; Gordon-Krajcer W; Ksiezak-Reding H
 CS Department of Pathology, Albert Einstein College of Medicine, Bronx, New
 York 10461, U.S.A.
 NC NS30027 (NINDS)
 NS35254 (NINDS)
 SO JOURNAL OF NEUROCHEMISTRY, (1997 Oct) 69 (4) 1548-58.

Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
EW 19980104
AB . . . subjected to treatment with either formic acid or guanidine.
Both

procedures effectively abolished the fibrillary structure of PHF but preserved PHF-tau **immunoreactivity** using a panel of **antibodies** that recognize nonphosphorylated and **phosphorylated** epitopes. These treatments also significantly increased the sensitivity of PHF-tau polypeptides to calpain proteolysis as shown by significant decreases in. . .

L4 ANSWER 11 OF 35 MEDLINE
AN 97392392 MEDLINE
DN 97392392
TI Identification of microtubule-associated protein tau isoforms in Alzheimer's paired helical filaments.
AU McLaughlin L; Zemlan F P; Dean G E
CS Alzheimer's Research Center, Department of Psychiatry, University of Cincinnati College of Medicine, OH 45267, USA.
NC AG01257 (NIA)
MH52959 (NIMH)
SO BRAIN RESEARCH BULLETIN, (1997) 43 (5) 501-8.
Journal code: B5M. ISSN: 0361-9230.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
AB . . . tau purified from control brains. Antibody Alz-50 was immunoreactive with PHF-tau or normal tau regardless of alkaline phosphatase treatment while **immunoreactivity** was only observed with dephosphorylated AD66 proteins. A second **phosphorylated** epitope on AD66 proteins but not PHF-tau or normal tau proteins was demonstrated with **antibody** PHF9. These data suggest that AD66 proteins represent a more phosphorylated form of tau than PHF-tau or normal tau proteins.. . .

L4 ANSWER 12 OF 35 MEDLINE
AN 97343976 MEDLINE
DN 97343976
TI Acute rise in the concentration of free cytoplasmic calcium leads to dephosphorylation of the microtubule-associated protein tau.
AU Adamec E; Mercken M; Beermann M L; Didier M; Nixon R A
CS Laboratories for Molecular Neuroscience, Mailman Research Center, McLean Hospital, Belmont, MA 02178, USA.. edamec@crcii.mclean.org
NC AG05604 (NIA)
AG10916 (NIA)
SO BRAIN RESEARCH, (1997 May 16) 757 (1) 93-101.
Journal code: B5L. ISSN: 0006-8993.

CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
EW 19971003
AB . . . led to tau protein dephosphorylation as indicated by an appearance of additional faster moving bands on Western immunoblots with
a
phosphorylation-independent antibody and an increase in the **tau-1 immunoreactivity** associated with the appearance of an additional faster moving band. Lowering the extracellular

concentration of Ca²⁺ to less than 1. . .

L4 ANSWER 13 OF 35 MEDLINE
AN 97268706 MEDLINE
DN 97268706
TI Familial multiple system tauopathy with presenile dementia: a disease
with abundant neuronal and glial tau filaments.
AU Spillantini M G; Goedert M; Crowther R A; Murrell J R; Farlow M R; Ghetti
B
CS Medical Research Council Cambridge Centre for Brain Repair, University of
Cambridge, United Kingdom.. mgs11@cam.ac.uk
NC NS29822 (NINDS)
P30 AG10133 (NIA)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF
AMERICA, (1997 Apr 15) 94 (8) 4113-8.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199707
AB . . . filaments that differ in diameter and periodicity from the
paired helical filaments of Alzheimer disease. They are stained by both
phosphorylation-independent and -dependent anti-**tau**
antibodies. Moreover, **tau immunoreactivity**
coexists with heparan sulfate in affected nerve and glial cells. Tau
protein extracted from filaments of familial multiple system tauopathy.

L4 ANSWER 14 OF 35 MEDLINE
AN 97244917 MEDLINE
DN 97244917
TI Neuritic plaques in the Lewy body variant of Alzheimer disease lack
paired helical filaments.
AU Samuel W; Crowder R; Hofstetter C R; Hansen L
CS Department of Neurosciences, University of California, San Diego, USA.
SO NEUROSCIENCE LETTERS, (1997 Feb 21) 223 (2) 73-6.
Journal code: N7N. ISSN: 0304-3940.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199708
AB . . . in having a neocortical predominance of diffuse and neuritic
plaques (NP), with very few neurofibrillary tangles (NFT). We
investigated the **immunoreactivity** of NP with a monoclonal **antibody**
against **paired helical filaments** (PHF)
composed of **phosphorylated** microtubule associated protein tau.
With routine thioflavin-S preparations, 12 LBV and 14 AD cases had
similar numbers of NP, but. . .

L4 ANSWER 15 OF 35 MEDLINE
AN 97114108 MEDLINE
DN 97114108
TI Plaque biogenesis in brain aging and Alzheimer's disease. I. Progressive
changes in phosphorylation states of paired helical filaments and
neurofilaments.
AU Su J H; Cummings B J; Cotman C W
CS Institute for Brain Aging and Dementia, University of California, Irvine
92697-4540, USA.

NC AG07918 (NIA)
 SO BRAIN RESEARCH, (1996 Nov 11) 739 (1-2) 79-87.
 Journal code: B5L. ISSN: 0006-8993.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199706
 AB . . . In the present study, we investigated whether PHF/tau-positive dystrophic neurites are located in all subtypes of plaques and whether swollen neurofilament-**immunoreactive** neurites are hyper-**phosphorylated**, using a battery of **antibodies** to PHF/**tau**, neurofilament, and beta-amyloid protein. PHF/**tau**-positive dystrophic neurites were present in and around nearly all subtypes of plaques, including small amyloid deposits, diffuse plaques, and perivascular. . .

L4 ANSWER 16 OF 35 MEDLINE
 AN 96397823 MEDLINE
 DN 96397823
 TI AD2, a phosphorylation-dependent monoclonal antibody directed against tau proteins found in Alzheimer's disease.
 AU Buee-Scherrer V; Condamines O; Mourton-Gilles C; Jakes R; Goedert M; Pau B; Delacourte A
 CS INSERM U422, Lille, France.
 SO BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1996 Jul) 39 (1-2) 79-88.
 Journal code: MBR. ISSN: 0169-328X.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199702
 AB . . . to detect the triplet not only in tau preparations but also in total brain homogenates from Alzheimer's disease patients. The **binding** of this monoclonal **antibody** to **tau** proteins is **phosphorylation** dependent. Characterization of this **antibody** allowed us to identify its epitope as containing **phosphorylated** Ser-396 with the participation of phosphorylated Ser-404. AD2 was also shown to label normal tau proteins from rapidly processed brain. . .

L4 ANSWER 17 OF 35 MEDLINE
 AN 96295034 MEDLINE
 DN 96295034
 TI Site-specific regulation of Alzheimer-like tau phosphorylation in living neurons.
 AU Burack M A; Halpain S
 CS Department of Neuroscience, University of Virginia, Charlottesville 22908, USA.
 NC GM07267 (NIGMS)
 SO NEUROSCIENCE, (1996 May) 72 (1) 167-84.
 Journal code: NZR. ISSN: 0306-4522.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199612
 AB . . . in adult brain. We examined the regulation of tau phosphorylation at some of these sites in rat brain using the **phosphorylation** state-dependent anti-**tau antibodies** AT8, Taul, and PHF1. The AT8 and PHF1 **antibodies** bind to **phosphorylated tau**, while Taul **binds** to unphosphorylated **tau**. Levels of tau reactive for AT8 were high only during the first postnatal week, with levels in adult declining to.

L4 ANSWER 18 OF 35 MEDLINE
 AN 96105463 MEDLINE
 DN 96105463
 TI Alzheimer's disease-type neurofibrillary degeneration in verrucose dysplasias of the cerebral cortex.
 AU Moran M A; Probst A; Navarro C; Gomez-Ramos P
 CS Department of Morphology, School of Medicine, Autonomous University of Madrid, Spain.
 SO ACTA NEUROPATHOLOGICA, (1995) 90 (4) 356-65.
 Journal code: 1CE. ISSN: 0001-6322.
 CY GERMANY: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199604
 AB . . . disorders and one with motor neuron disease), are shown to present neurofibrillary degeneration of Alzheimer's disease type. This neurofibrillary degeneration **immunoreacted** with **antibodies** against abnormally **phosphorylated tau** (5E2 and AT8), disclosed acetyl- and butyrylcholinesterase activity, and was consistently stained with thioflavin-S. Cortical dysplasias, found either as isolated. . .

L4 ANSWER 19 OF 35 MEDLINE
 AN 96034852 MEDLINE
 DN 96034852
 TI Secreted beta-APP stimulates MAP kinase and phosphorylation of tau in neurons.
 AU Greenberg S M; Kosik K S
 CS Department of Neurology, Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115, USA.
 NC AG06601 (NIA)
 SO NEUROBIOLOGY OF AGING, (1995 May-Jun) 16 (3) 403-7; discussion 407-8.
 Journal code: NX5. ISSN: 0197-4580.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199601
 AB . . . neurons, we found that exposure to beta-APP activated MAP kinase 4 and 7 days but not 1 day after plating. **Phosphorylation** of **tau** in neurons was measured by **immunoreactivity** with the AT8 **antibody**, which recognizes a **phosphorylated** epitope present in **tau** from **paired helical filaments**. We found that activation of MAP kinase in neurons was associated with increased amounts of AT8-reactive tau. These results support. . .

L4 ANSWER 20 OF 35 MEDLINE
 AN 95370202 MEDLINE
 DN 95370202
 TI Detection of phosphorylated Ser262 in fetal tau, adult tau, and paired helical filament tau.
 AU Seubert P; Mawal-Dewan M; Barbour R; Jakes R; Goedert M; Johnson G V; Litersky J M; Schenk D; Lieberburg I; Trojanowski J Q; et al
 CS Athena Neurosciences, Incorporated, South San Francisco, California 94080, USA.
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Aug 11) 270 (32) 18917-22.
 Journal code: HIV. ISSN: 0021-9258.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals

EM 199511
 AB . . . adult brain tau. However, Ser262 has been suggested to be uniquely phosphorylated in PHF-tau and a key regulator of the **binding** of tau to microtubules. For these reasons, we generated a monoclonal **antibody** (12E8) specific for **phosphorylated** Ser262 and showed that 12E8 **binds** to PHF-tau, rat and human fetal brain tau, as well as to rapidly processed adult rat and biopsy-derived human brain. . .

L4 ANSWER 21 OF 35 MEDLINE
 AN 95343726 MEDLINE
 DN 95343726
 TI Ganglioglioma with neurofibrillary tangles (NFTs): neoplastic NFTs share antigenic determinants with NFTs of Alzheimer's disease.
 AU Soffer D; Umansky F; Goldman J E
 CS Department of Pathology (Neuropathology), Hadassah Medical Center, Jerusalem, Israel.
 SO ACTA NEUROPATHOLOGICA, (1995) 89 (5) 451-3.
 Journal code: 1CE. ISSN: 0001-6322.
 CY GERMANY: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199510
 AB . . . type. The NFTs in the tumor were argyrophilic and Congo red and thioflavin-S positive. Immunohistochemically, the NFTs were reactive with **antibodies** to phosphorylated neurofilament protein, PHF/**tau** and ubiquitin. The demonstration in the neoplasm of abnormally **phosphorylated** and ubiquitinated cytoskeletal components, similar in morphology and in **immunoreactivity** to those seen in NFTs of Alzheimer's disease, suggest that similar pathogenetic mechanisms may operate in both conditions.

L4 ANSWER 22 OF 35 MEDLINE
 AN 95275281 MEDLINE
 DN 95275281
 TI Preparation of tau from the peripheral nerve: presence of insoluble low molecular weight tau with high phosphorylation.
 AU Sun X; Tashiro T; Hirai S; Yamamoto H; Miyamoto E; Komiya Y
 CS Department of Molecular and Cellular Neurobiology, Gunma University School of Medicine, Maebashi, Japan..
 SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1995 May 16) 210 (2) 338-44.
 Journal code: 9Y8. ISSN: 0006-291X.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199508
 AB . . . these axonal LMW isoforms corresponded to the most acidic species among the large number of isoforms found in brain microtubule-associated **tau**. **Immunoreactivities** towards **phosphorylation**-dependent **antibody tau-1** and the two anti-phosphopeptide **antibodies** (PP1 and PP2) indicate that PNS axonal **tau** is highly **phosphorylated** at Ser190, Ser193, and Ser387, which are the sites shown to be phosphorylated in fetal brain tau and tau comprising. . .

L4 ANSWER 23 OF 35 MEDLINE
 AN 95227684 MEDLINE
 DN 95227684
 TI Tau immunoreactivity associated with aluminum maltolate-induced neurofibrillary degeneration in rabbits.

AU Savory J; Huang Y; Herman M M; Reyes M R; Wills M R
 CS Department of Pathology, University of Virginia Health Sciences Center,
 Charlottesville 22908.
 SO BRAIN RESEARCH, (1995 Jan 16) 669 (2) 325-9.
 Journal code: B5L. ISSN: 0006-8993.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199507
 AB Intracisternal administration of aluminum maltolate to rabbits produces a
 marked argyrophilic neurofibrillary degeneration (NFD) which is also
immunoreactive for both **phosphorylated** and non-
phosphorylated microtubule associated protein **tau**. Using
 tissue fixation in PBF, the monoclonal **antibodies** Tau-2 and AT8
 stain the NFD. Dephosphorylation markedly reduces the positivity of AT8.
 Using PLP-fixed tissue, monoclonal antibody Tau-1 also. . .

L4 ANSWER 24 OF 35 MEDLINE

AN 94368433 MEDLINE

DN 94368433

TI Familial Gerstmann-Straussler-Scheinker disease with neurofibrillary
 tangles.

AU Ghetti B; Tagliavini F; Giaccone G; Bugiani O; Frangione B; Farlow M R;
 Dlouhy S R

CS Indiana University School of Medicine, Indianapolis.

NC R01-NS29822 (NINDS)

SO MOLECULAR NEUROBIOLOGY, (1994 Feb) 8 (1) 41-8. Ref: 25

Journal code: AH6. ISSN: 0893-7648.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LA English

FS Priority Journals

EM 199412

AB . . . the amyloid contains an 11-kDa peptide, an amyloidogenic
 degradation product of the prion protein. The neurofibrillary tangles are
 composed of **paired helical filaments** and
immunoreact with **antibody** to A68, an abnormally
phosphorylated form of the microtubule-associated protein tau. In
 these families, the disease is caused by a point mutation in the PRNP. .
 .

L4 ANSWER 25 OF 35 MEDLINE

AN 94337595 MEDLINE

DN 94337595

TI Neuronal cytoskeletal abnormalities in human cerebral cortical
 dysplasia.

AU Duong T; De Rosa M J; Poukens V; Vinters H V; Fisher R S

CS Indiana University School of Medicine, Terre Haute Center for Medical
 Education at Indiana State University 47809.

NC HD 07032 (NICHD)

NS28383 (NINDS)

NS24596 (NINDS)

+

SO ACTA NEUROPATHOLOGICA, (1994) 87 (5) 493-503.

Journal code: ICE. ISSN: 0001-6322.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199411

AB . . . seen in hypertrophic neurons of cortical dysplasia. These
 neurofilamentous accumulations of cortical dysplasia as well as AD
 tangles

also displayed **immunoreactivity** with **antibodies** against **phosphorylated** and non-**phosphorylated** neuro-filament epitopes, **tau** and ubiquitin. Only the AD tangles, however, were **immunoreactive** to the antiserum to PHF. These results replicate and extend our previous findings that the neurofibrillary accumulations in cerebral cortical. . .

L4 ANSWER 26 OF 35 MEDLINE
AN 94332649 MEDLINE
DN 94332649
TI Glutamate increases tau phosphorylation in primary neuronal cultures from fetal rat cerebral cortex.
AU Sindou P; Lesort M; Couratier P; Yardin C; Esclaire F; Hugon J
CS Unite de Neurobiologie Cellulaire, Faculte de Medecine, Limoges, France..
SO BRAIN RESEARCH, (1994 May 16) 646 (1) 124-8.
Journal code: B5L. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199411
AB . . . report that glutamate an excitatory neurotransmitter and also a potent excitotoxin produces in primary neuronal cultures a rapid increase in **phosphorylated Tau** protein **immunoreactivity** using AT8 **antibody**. Glutamate augments neuronal **Tau immunoreactivity** by 225% using laser confocal immunocytochemistry and by 355% on immunoblot analysis. This experimental model of Tau protein modifications could. . .

L4 ANSWER 27 OF 35 MEDLINE
AN 94074679 MEDLINE
DN 94074679
TI A cdc2-related kinase PSSALRE/cdk5 is homologous with the 30 kDa subunit of tau protein kinase II, a proline-directed protein kinase associated with microtubule.
AU Kobayashi S; Ishiguro K; Omori A; Takamatsu M; Arioka M; Imahori K; Uchida T
CS Mitsubishi Kasei Institute of Life Sciences, Tokyo, Japan.
SO FEBS LETTERS, (1993 Dec 6) 335 (2) 171-5.
Journal code: EUH. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199403
AB . . . and 23 kDa subunits. The 30 kDa subunit of TPKII can be regarded as a catalytic subunit because of its ATP-**binding** activity. **Antibodies** directed against TPKII-**phosphorylated tau** also reacted with **tau phosphorylated** by cdc2 kinase obtained from starfish oocytes, indicating that TPKII and cdc2 kinase phosphorylate the same sites. We determined the. . .

L4 ANSWER 28 OF 35 MEDLINE
AN 94065788 MEDLINE
DN 94065788
TI Developmental changes in tau phosphorylation: fetal tau is transiently phosphorylated in a manner similar to paired helical filament-tau characteristic of Alzheimer's disease.
AU Brion J P; Smith C; Couck A M; Gallo J M; Anderton B H
CS Laboratory of Pathology and Electron Microscopy, Universite Libre de Bruxelles, Belgium.
SO JOURNAL OF NEUROCHEMISTRY, (1993 Dec) 61 (6) 2071-80.

Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199403
AB . . . could be distinguished on sodium dodecyl sulfate-polyacrylamide gel electrophoresis and the slower migrating species was recognized by all

of the PHF-**tau**-specific **antibodies**. Moreover, this **immunoreactivity** was shown to be **phosphorylation** dependent. Our observations suggest that the abnormal phosphorylation of tau in Alzheimer's disease may be the result of reactivation of. . .

L4 ANSWER 29 OF 35 MEDLINE
AN 93327169 MEDLINE
DN 93327169
TI Phosphorylation of tau by proline-directed protein kinase (p34cdc2/p58cyclin A) decreases tau-induced microtubule assembly and antibody SMI33 reactivity.
AU Scott C W; Vulliet P R; Caputo C B
CS Pharmacology Department, ICI Americas Inc., Wilmington, DE 19897-2500..
SO BRAIN RESEARCH, (1993 May 21) 611 (2) 237-42.
Journal code: B5L. ISSN: 0006-8993.

CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199310
AB . . . assembly but had no effect on the final extent of microtubule formation or on the rate of cold-induced microtubule disassembly. **Phosphorylation of tau** by the proline-directed protein kinase completely blocked **immunoreactivity** with **antibody** SMI33. **Phosphorylation** did not create the epitopes for the phosphate-dependent antibodies SMI31 or SMI34. Antibody SMI33 recognizes neurofibrillary tangles after treatment with. . .

L4 ANSWER 30 OF 35 MEDLINE
AN 93238908 MEDLINE
DN 93238908
TI Phosphorylated tau epitope of Alzheimer's disease is coupled to axon development in the avian central nervous system.
AU Pope W; Enam S A; Bawa N; Miller B E; Ghanbari H A; Klein W L
CS Department of Neurobiology and Physiology, Northwestern University, Evanston, Illinois 60201.
SO EXPERIMENTAL NEUROLOGY, (1993 Mar) 120 (1) 106-13.
Journal code: EQF. ISSN: 0014-4886.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199307
AB The monoclonal **antibody** PHF-1 recognizes **phosphorylated** tau isoforms present in **paired helical filaments** of Alzheimer's disease. We have found that PHF-1 **immunoreactivity** is present in chick brain, which expresses three major PHF-1-reactive proteins at the same molecular weights seen in humans. The. . .

L4 ANSWER 31 OF 35 MEDLINE
AN 93125851 MEDLINE
DN 93125851
TI Glycogen synthase kinase-3 induces Alzheimer's disease-like phosphorylation of tau: generation of paired helical filament epitopes and neuronal localisation of the kinase.

AU Hanger D P; Hughes K; Woodgett J R; Brion J P; Anderton B H
 CS Department of Neuroscience, Institute of Psychiatry, London, UK.
 SO NEUROSCIENCE LETTERS, (1992 Nov 23) 147 (1) 58-62.
 Journal code: N7N. ISSN: 0304-3940.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199304
 AB Glycogen synthase kinase-3 (GSK-3) reduced the mobility of human tau on SDS-PAGE, prevented **binding** of the monoclonal **antibody** (mAb), **Tau.1**, and induced **binding** of the mAb 8D8. Recombinant tau **phosphorylated** by GSK-3 aligned on SDS-PAGE with the abnormally phosphorylated tau (PHF-tau) associated with the paired helical filaments in Alzheimer's disease. . . .

L4 ANSWER 32 OF 35 MEDLINE
 AN 93054555 MEDLINE
 DN 93054555
 TI Proline-directed phosphorylation of human Tau protein.
 AU Vulliamt R; Halloran S M; Brion J P; Smith A J; Lee G
 CS Department of Veterinary Pharmacology and Toxicology, School of Veterinary Medicine, University of California, Davis 95616..
 NC 1R01-NS28765-01 (NINDS)
 GM39300 (NIGMS)
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1992 Nov 5) 267 (31) 22570-4.
 Journal code: HIV. ISSN: 0021-9258.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199302
 AB . . . that has been found to be required for the in vivo co-localization of tau protein to microtubules. Two other putative **phosphorylation** sites are located within the identified epitope of the monoclonal **antibody** Tau-1. **Phosphorylation** of these sites altered the **immunoreactivity** of tau to **Tau-1 antibody**. Since the neuronal microtubule-associated protein tau is multiply **phosphorylated** in Alzheimer's disease, and Tau-1 **immunoreactivity** is similarly reduced in neurofibrillary tangles and enhanced after dephosphorylation, phosphorylation at one or more of these sites may correlate. . . .

L4 ANSWER 33 OF 35 MEDLINE
 AN 92362885 MEDLINE
 DN 92362885
 TI Implication of brain cdc2 and map2 kinases in the phosphorylation of tau protein in Alzheimer's disease.
 AU Ledesma M D; Correas I; Avila J; Diaz-Nido J
 CS Centro de Biologia Molecular (CSIC-UAM), Universidad Autonoma, Madrid, Spain.
 SO FEBS LETTERS, (1992 Aug 17) 308 (2) 218-24.
 Journal code: EUH. ISSN: 0014-5793.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199211
 AB . . . purification from rat brain extracts. The phosphorylation sites are located on the tau molecule both upstream and downstream of the tubulin-**binding** motifs. A synthetic peptide comprising residues 194-213 of the tau sequence, which contains the epitope recognized by the monoclonal **antibody** tau-1, is also efficiently **phosphorylated** in vitro by cdc2 and MAP2 kinases. Phosphorylation of this peptide markedly reduces its interaction with the antibody tau-1,

as. . .

L4 ANSWER 34 OF 35 MEDLINE
AN 89010837 MEDLINE
DN 89010837
TI Neurofibrillary tangles and senile plaques in aged bears [published
erratum appears in J Neuropathol Exp Neurol 1989 Jul;48(4):497] [see
comments].
CM Comment in: J Neuropathol Exp Neurol 1990 Mar;49(2):190-2
AU Cork L C; Powers R E; Selkoe D J; Davies P; Geyer J J; Price D L
CS Division of Comparative Medicine, Johns Hopkins University School of
Medicine, Baltimore, Maryland 21205-2182.
NC AG 05146 (NIA)
NS 07179 (NINDS)
AG 06173 (NIA)
+
SO JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, (1988 Nov) 47 (6)
629-41.
Journal code: JBR. ISSN: 0022-3069.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198901
AB . . . similar to those occurring in humans. An aged Asiatic brown bear
had NFT, composed of straight 10-16-nm filaments, that were
immunoreactive with antibodies directed against:
phosphorylated epitopes of neurofilaments (NF); **tau**; A68
(a protein enriched in AD); and an antigen associated with paired helical
filaments (PHF). An aged pig had . . .

L4 ANSWER 35 OF 35 MEDLINE
AN 88080542 MEDLINE
DN 88080542
TI Phosphorylation determines two distinct species of Tau in the central
nervous system.
AU Papasozomenos S C; Binder L I
CS Department of Pathology, University of Texas Medical School, Houston
77225.
NC NS22453 (NINDS)
AG06969 (NIA)
SO CELL MOTILITY AND THE CYTOSKELETON, (1987) 8 (3) 210-26.
Journal code: CRD. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198804
AB . . . following phosphatase treatment of tissue. We report here that a
significant quantity of tau in the central nervous system is
phosphorylated in situ at or near the **Tau-1** epitope,
preventing the **binding** of **Tau-1 antibody**. Upon
removal of this/these phospho group(s), however, Tau-1 was observed in
the somatodendritic compartment of neurons as well as in . . .

Ser (20) Phospho (20) At (20) Ab

L2 ANSWER 1 OF 16 MEDLINE
AN 2002328969 MEDLINE
DN 22066548 PubMed ID: 12071639
TI Colocalization and fluorescence resonance energy transfer between cdk5 and AT8 suggests a close association in pre-neurofibrillary tangles and neurofibrillary tangles.
AU Augustinack Jean C; Sanders Judith L; Tsai Li-Huei; Hyman Bradley T
CS Department of Neurology, Harvard Medical School, Massachusetts General Hospital, Charlestown 02129, USA.
NC AG08487 (NIA)
NS 07484-01 (NINDS)
SO JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, (2002 Jun) 61 (6) 557-64.
Journal code: 2985192R. ISSN: 0022-3069.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200207
ED Entered STN: 20020620
Last Updated on STN: 20020709
Entered Medline: 20020708
AB Cyclin-dependent kinase 5 (cdk5) is a serine/threonine kinase that, when activated, induces neurite outgrowth. Recent in vitro studies have shown that cdk5 phosphorylates tau at serine 199, serine 202, and threonine 205 and that p25, an activator of cdk5, is increased in **Alzheimer** disease (AD). Since tau is hyperphosphorylated at these sites in neurofibrillary tangles, we examined brain tissue from patients with AD and normal elderly control cases to determine whether cdk5 and these phosphoepitopes colocalize in neurofibrillary tangles. Adjacent temporal lobe sections were double immunostained with a polyclonal anti-cdk5 and monoclonal AT8 (which recognizes **phosphorylated serine** 199, **serine** 202, and threonine 205 in tau) **antibodies**. A subset of AT8 **phosphotau**-positive neurons was immunoreactive for cdk5 in entorhinal (area 28) and perirhinal (area 35) cortices and CA1 of the hippocampus. We assessed the ratio of cdk5-positive cells to AT8-positive cells and found that there is a higher degree of colocalization in pre-neurofibrillary tangles as opposed to intraneuronal and extraneuronal neurofibrillary tangles. We further examined colocalization using fluorescence resonance energy transfer. This suggests a close, stable intermolecular association between cdk5 and phosphorylated tau, consistent with phosphorylation of tau by cdk5 in AD brain.

L2 ANSWER 4 OF 16 MEDLINE
 AN 97342807 MEDLINE
 DN 97342807 PubMed ID: 9199504
 TI Phosphorylation of microtubule-associated protein tau by stress-activated protein kinases.
 AU Goedert M; Hasegawa M; Jakes R; Lawler S; Cuenda A; Cohen P
 CS MRC Laboratory of Molecular Biology, Cambridge, UK.
 SO FEBS LETTERS, (1997 Jun 2) 409 (1) 57-62.
 Journal code: 0155157. ISSN: 0014-5793.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199707
 ED Entered STN: 19970721
 Last Updated on STN: 19980206
 Entered Medline: 19970708
 AB The paired helical filament, which comprises the major fibrous element of the neurofibrillary lesions of **Alzheimer's** disease, is composed of hyperphosphorylated microtubule-associated protein tau. Many of the hyperphosphorylated sites in tau are serine/threonine-prolines. Here we show that the stress-activated protein (SAP) kinases SAPK1gamma (also called JNK1), SAPK2a (also called p38, RK, CSBPs, Mpk2 and Mxi2), SAPK2b (also called p38beta), SAPK3 (also called ERK6 and p38gamma) and SAPK4 **phosphorylate** tau at many **serine**/threonine-prolines, as assessed by the generation of the epitopes of **phosphorylation**-dependent anti-tau **antibodies**. Based on initial rates of phosphorylation, tau was found to be a good substrate for SAPK4 and SAPK3, a reasonable substrate for SAPK2b and a relatively poor substrate for SAPK2a and SAPK1gamma. Phosphorylation of tau by SAPK3 and SAPK4 resulted in a marked reduction in its ability to promote microtubule assembly. These findings double the number of candidate protein kinases for the hyperphosphorylation of tau in **Alzheimer's** disease and other neurodegenerative disorders.

L2 ANSWER 5 OF 16 MEDLINE
 AN 97238112 MEDLINE
 DN 97238112 PubMed ID: 9084448
 TI Stress-activated protein kinase/c-jun N-terminal kinase phosphorylates tau protein.
 AU Reynolds C H; Utton M A; Gibb G M; Yates A; Anderton B H
 CS Department of Neuroscience, Institute of Psychiatry, London, England.
 SO JOURNAL OF NEUROCHEMISTRY, (1997 Apr) 68 (4) 1736-44.
 Journal code: 2985190R. ISSN: 0022-3042.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199704
 ED Entered STN: 19970507
 Last Updated on STN: 19970507
 Entered Medline: 19970428
 AB A proportion of the neuronal microtubule-associated protein (MAP) tau is highly phosphorylated in foetal and adult brain, whereas the majority of tau in the neurofibrillary tangles of **Alzheimer's** patients is hyperphosphorylated; many of the phosphorylation sites are serines or threonines followed by prolines. Several kinases phosphorylate tau at such sites in vitro. We have now shown that purified recombinant stress-activated protein kinase/c-Jun N-terminal kinase, a proline-directed kinase of the MAP kinase extended family, **phosphorylates** recombinant tau in vitro on threonine and **serine** residues. Western blots using **antibodies** to **phosphorylation**-dependent tau epitopes demonstrated that **phosphorylation** occurs in both of the main **phosphorylated** regions of tau protein. Unlike glycogen synthase kinase-3, the c-Jun N-terminal kinase readily phosphorylates Thr205 and Ser422, which are more highly phosphorylated in **Alzheimer** tau than in foetal or adult tau. Glycogen synthase kinase-3 may preferentially phosphorylate the sites found physiologically, in foetal and to a smaller extent in adult tau, whereas stress-activated/c-Jun N-terminal kinase and/or other members of the extended MAP kinase family may be responsible for pathological proline-directed phosphorylations. Inflammatory processes in **Alzheimer** brain might therefore contribute directly to the pathological formation of the hyperphosphorylated tau found in neurofibrillary tangles.

L2 ANSWER 6 OF 16 MEDLINE
 AN 97047189 MEDLINE
 DN 97047189 PubMed ID: 8892109
 TI Monoclonal **antibody** PHF-9 recognizes **phosphorylated serine** 404 of tau protein and labels paired helical filaments.
 AU Zemlan F P; Dean G E
 CS Department of Psychiatry, University of Cincinnati College of Medicine, Ohio 45267-0559, USA.
 NC AG0157 (NIA)
 MH-52958 (NIMH)
 SO JOURNAL OF NEUROSCIENCE RESEARCH, (1996 Oct 1) 46 (1) 90-7.
 Journal code: 7600111. ISSN: 0360-4012.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199705
 ED Entered STN: 19970523
 Last Updated on STN: 19980206
 Entered Medline: 19970513
 AB Paired helical filaments (PHFs) purified from **alzheimer's** brain consist of hyperphosphorylated microtubule-associated protein tau. In PHF, phosphorylation occurs at ser/thr tau residues. Several of these ser/thr phosphorylation sites lie immediately C-terminal to the tau tubulin binding domain. The C-terminal ser396 to thr413 tau region contains two or more phosphorylated residues and eight possible ser/thr phosphorylation sites. Immunologic studies and mass spectroscopy have identified ser396 as one of the phosphorylation sites but identification of more C-terminal phosphorylated residues has been hampered by the lack of monoclonal antibodies (Mabs) that recognize defined epitopes in this region. We have raised Mabs against PHF purified from **Alzheimer's** brain. One of these Mabs, PHF-9, showed phosphorylation-dependent binding to purified PHF and recognized a phosphorylated epitope in the C-terminal portion of cyanogen bromide-digested PHF. Epitope mapping studies employing synthetic tau phosphopeptides indicated that PHF-9 labeled a 13-mer tau peptide phosphorylated at ser404 but not the corresponding non-phosphorylated peptide. PHF-9 demonstrated no immunoreactivity with a synthetic peptide phosphorylated at ser396 indicating that the PHF-9 epitope is C-terminal to ser396. In conclusion, the present study describes a Mab, PHF-9, which recognizes phosphorylated ser404 of tau independently of phosphorylated ser396 and indicates that tau ser404 is phosphorylated in PHF.

L2 ANSWER 7 OF 16 MEDLINE
 AN 97013371 MEDLINE
 DN 97013371 PubMed ID: 9147412
 TI Modifications of neuronal phosphorylated tau immunoreactivity induced by NMDA toxicity.
 AU Couratier P; Lesort M; Sindou P; Esclaïre F; Yardin C; Hugon J
 CS Unite de Neurobiologie Cellulaire, Laboratoire d'Histologie Faculte de Medecine, France.
 SO MOLECULAR AND CHEMICAL NEUROPATHOLOGY, (1996 Apr) 27 (3) 259-73.
 Journal code: 8910358. ISSN: 1044-7393.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199705
 ED Entered STN: 19970523
 Last Updated on STN: 19980206
 Entered Medline: 19970512
 AB Glutamate toxicity has been involved in the pathophysiology of a large variety of neurodegenerative disorders. Tau Protein is a micro-tubule-associated protein that promotes microtubule polymerization and stabilization. Phosphorylated tau protein accumulates in paired helical neurofilaments, the major constituent of neurofibrillary tangles observed in the brain of patients suffering from **Alzheimer** disease (AD). In this study, using confocal laser microscopy and immunoblot analysis, we report that acute (500 μ M for 15 min) or chronic (20 μ M for 16 h) N-methyl-D-aspartate (NMDA) neuronal toxicities modify the immunoreactivity of **phosphorylated** tau. Neuronal degeneration produced by N-methyl-D-aspartate is associated with an augmented immunolabeling of **phosphorylated** tau proteins at **serine 202** (AT8 **antibody**) as observed in paired helical neurofilaments. This finding could help to determine the cellular mechanisms at the origin of neuronal degeneration associated with modifications of phosphorylated tau immunoreactivity produced by receptor-mediated extracellular signals.

L2 ANSWER 8 OF 16 MEDLINE
 AN 96432851 MEDLINE
 DN 96432851 PubMed ID: 8835879
 TI Sequential changes of tau-site-specific phosphorylation during development of paired helical filaments.
 AU Kimura T; Ono T; Takamatsu J; Yamamoto H; Ikegami K; Kondo A; Hasegawa M; Ihara Y; Miyamoto E; Miyakawa T
 CS Division of Clinical Research, National Kikuchi Hospital, Kumamoto, Japan.
 SO DEMENTIA, (1996 Jul-Aug) 7 (4) 177-81.
 Journal code: 9010348. ISSN: 1013-7424.
 CY Switzerland
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199701
 ED Entered STN: 19970219
 Last Updated on STN: 19980206
 Entered Medline: 19970130
 AB It has been reported that many tau sites in neurofibrillary tangles (NFT) are abnormally phosphorylated. We investigated the phosphorylation of tau in the hippocampus of nondemented patients and **Alzheimer's** disease patients by immunostaining with five site-specific **antibodies** against **phosphorylated** tau. In the pretangle stage, tau in neuropil threads was **phosphorylated** at **serines** 199, 202 and 409, numbered according to the longest human tau isoform, whereas tau in some neuronal soma was **phosphorylated** at serines 199, 202, 409 and 422. Tau at the stage of NFT was phosphorylated at serine 396 and threonine 231 in addition to serines 199, 202, 409 and 422. In the advanced stage, tau in ghost tangles was phosphorylated mainly at serine 396. These results suggest that the phosphorylation of each site in tau differs among the maturing stages of neurofibrillary change and that abnormal phosphorylation of tau in the neuronal soma occurs at 199, 202, 409 and 422 earlier than at threonine 231 and serine 396.

L2 ANSWER 10 OF 16 MEDLINE
 AN 95244033 MEDLINE
 DN 95244033 PubMed ID: 7537044
 TI Tyrosine- versus serine-phosphorylation leads to conformational changes in a synthetic tau peptide.
 AU Fabian H; Otvos L Jr; Szendrei G I; Lang E; Mantsch H H
 CS Institute for Biochemistry, Humboldt University Berlin, Germany.
 NC AG-10670 (NIA)
 SO JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS, (1994 Dec) 12 (3) 573-9.
 Journal code: 8404176. ISSN: 0739-1102.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199505
 ED Entered STN: 19950608
 Last Updated on STN: 19980206
 Entered Medline: 19950530
 AB One of the major immunodominant epitopes of the paired helical filaments (PHF) of **Alzheimer's** disease is the peptide sequence GAEIVYKSPVVS GD (T3), comprising amino acids 389-402 of the microtubule-associated protein, tau, when it is **phosphorylated** at the first **serine** residue. While the corresponding anti-PHF monoclonal **antibody** recognizes the peptide **phosphorylated** at either **serine**, it does not recognize the tyrosine-**phosphorylated** peptide. Here we describe the effect of **serine-** versus tyrosine-**phosphorylation** on the conformation of a synthetic tau peptide. While adding a phosphate to the serine residue has practically no impact on the structure of the non-phosphorylated peptide, phosphorylation of the tyrosine results in considerable conformational changes.

L2 ANSWER 11 OF 16 MEDLINE
 AN 95205458 MEDLINE
 DN 95205458 PubMed ID: 7534834
 TI Monoclonal **antibody** PHF-1 recognizes tau protein
 phosphorylated at **serine** residues 396 and 404.
 AU Otvos L Jr; Feiner L; Lang E; Szendrei G I; Goedert M; Lee V M
 CS Wistar Institute, Philadelphia, PA 19104.
 NC AG-09215 (NIA)
 AG-10670 (NIA)
 SO JOURNAL OF NEUROSCIENCE RESEARCH, (1994 Dec 15) 39 (6) 669-73.
 Journal code: 7600111. ISSN: 0360-4012.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199504
 ED Entered STN: 19950504
 Last Updated on STN: 19980206
 Entered Medline: 19950425
 AB The microtubule-associated protein tau is hyperphosphorylated in the
 paired helical filaments (PHFs) of **Alzheimer's** disease.
 Immunological and direct chemical studies have identified Ser396 and
 Ser404 as two of the phosphorylated sites. Previously, we have
 demonstrated, using synthetic tau peptides containing phosphorylated
 Ser396, that this site is recognized by the monoclonal antibody PHF-1. The
 present study extends this observation by showing that PHF-1 recognizes
 tau peptides containing either individually phosphorylated Ser396 or
 Ser404, but that there is a > 10-fold increase in the sensitivity of
 detection of tau peptides by PHF-1 when both serines are phosphorylated.
 The recognition of singly or doubly phosphorylated Ser396 and Ser404 in
 tau by PHF-1 can also be demonstrated in Chinese hamster ovary cells
 transfected with full-length wild-type tau constructs or mutant constructs
 with Ala substituted for Ser396 or Ser404. We conclude that the PHF-1
 epitope contains both phosphorylated Ser396 and Ser404.

L2 ANSWER 13 OF 16 MEDLINE
 AN 94057830 MEDLINE
 DN 94057830 PubMed ID: 7694533
 TI Microtubule-associated protein tau, paired helical filaments, and phosphorylation.
 AU Mandelkow E M; Biernat J; Drewes G; Steiner B; Lichtenberg-Kraag B; Wille H; Gustke N; Mandelkow E
 CS Max-Planck-Unit for Structural Molecular Biology, Hamburg, Germany.
 SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1993 Sep 24) 695 209-16.
 Ref: 18
 Journal code: 7506858. ISSN: 0077-8923.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LA English
 FS Priority Journals
 EM 199312
 ED Entered STN: 19940117
 Last Updated on STN: 19980206
 Entered Medline: 19931210
 AB This paper summarizes our recent studies on microtubule-associated protein tau and its pathological state resembling that of the paired helical filaments of **Alzheimer's** disease. The **Alzheimer**-like state of tau protein can be identified and analyzed in terms of certain **phosphorylation** sites and **phosphorylation**-dependent **antibody** epitopes. It can be induced by protein kinases which tend to **phosphorylate serine** or threonine residues followed by a proline; this includes mitogen-activated protein kinase (MAPK) and glycogen-synthase kinase 3 (GSK-3). Both of these are tightly associated with microtubules as well as with paired helical filaments. Structurally, tau appears as a rod-like molecule; it tends to self-associate into dimers whose monomers are antiparallel. Constructs of truncated tau made up of antiparallel dimers of the microtubule binding domain can be assembled into paired helical filaments in vitro.

L2 ANSWER 14 OF 16 MEDLINE
 AN 93262939 MEDLINE
 DN 93262939 PubMed ID: 7684177
 TI Phosphorylated tau immunoreactivity of granulovacuolar bodies (GVB) of **Alzheimer's** disease: localization of two amino terminal tau epitopes in GVB.
 AU Dickson D W; Liu W K; Kress Y; Ku J; DeJesus O; Yen S H
 CS Department of Pathology (Neuropathology), Albert Einstein College of Medicine, Bronx, NY 10461.
 NC AG01136 (NIA)
 AG04145 (NIA)
 AG60803 (NIA)
 SO ACTA NEUROPATHOLOGICA, (1993) 85 (5) 463-70.
 Journal code: 0412041. ISSN: 0001-6322.
 CY GERMANY: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199306
 ED Entered STN: 19930625
 Last Updated on STN: 19980206
 Entered Medline: 19930615
 AB An immunocytochemical study of **Alzheimer's** disease hippocampus with a panel of anti-tau antibodies revealed two antibodies that stained granulovacuolar bodies (GVB) in pyramidal neurons of Ammon's horn. These two affinity-purified anti-tau antibodies were raised in rabbits against synthetic peptides homologous to sequences (amino acids 44-55 and 75-87) in the 58 amino acid insert in the amino terminus of the longest form of human tau. This region is homologous to exons 2 and exon 3 of bovine tau. The exon 2 peptide contains a **serine** (amino acid residue 46), which has been shown to be a **phosphorylated** site in paired helical filaments. **Antibodies** to a nonphosphorylated exon 2 peptide failed to immunostain GVB, but those to the phosphopeptide consistently stained GVB. Staining, however, was most consistent with the antibody to the exon 3 sequence. As in previous studies, GVB were also stained by RT97, a neurofilament **antibody** whose epitope in tau appears to be a **phosphorylated** site in or near exon 2, perhaps at **serine** residue 46 (Brion et al. 1992). **Antibodies** to epitopes in the amino terminus, mid-region and carboxy terminus of tau failed to consistently stain GVB. More often they produced staining around the periphery of the GVB, giving the appearance of an "empty vacuole." Most GVB were also immunoreactive with an antibody to ubiquitin. The results are consistent with the hypothesis that GVB are derived from sequestered altered tau possibly mediated by ubiquitin. The failure to detect most regions of tau in GVB is consistent with the idea that tau is partially degraded or highly modified in GVB.

L2 ANSWER 15 OF 16 MEDLINE
 AN 93252838 MEDLINE
 DN 93252838 PubMed ID: 8486651
 TI Locations and immunoreactivities of phosphorylation sites on bovine and porcine tau proteins and a PHF-tau fragment.
 AU Poulter L; Barratt D; Scott C W; Caputo C B
 CS Biotechnology Department, ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire.
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 May 5) 268 (13) 9636-44.
 Journal code: 2985121R. ISSN: 0021-9258.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199306
 ED Entered STN: 19930618
 Last Updated on STN: 19930618
 Entered Medline: 19930604
 AB Tau protein is a phosphorylated neuronal microtubule-associated protein. Tau protein is also present in the major pathological lesions of **Alzheimer's** disease in an insoluble hyperphosphorylated state as paired helical filaments (PHFs). We have investigated the phosphorylation state of control taus and a fragment of PHF-tau. Tau samples were digested with protease, separated by reversed-phase high-performance liquid chromatography, and analyzed by mass spectrometry and Edman microsequencing. The serine homologous with S404 of human tau 441 was phosphorylated on bovine and porcine tau and up to two phosphates were present on a peptide of amino acids 182-240 of bovine tau (193-251 of human tau 441). The serine within the KSPV motif was not phosphorylated on bovine or porcine tau. PHF-tau fragments, isolated from pronase-treated PHFs encompassed a 93-amino acid region within the microtubule binding domain. Enzymatic digestion and mass spectrometric analysis showed no phosphate was present and a second carboxyl terminus was identified at E380. Antibodies T3P and SMI34, which recognize PHF-tau and peptides phosphorylated at the sequence KSPV, both reacted with bovine and porcine tau even though the KSPV sequence was not **phosphorylated**. These data indicate that the 93-amino acid sequence of F5.5 tau from PHFs is not **phosphorylated**, and the **serine** equivalent to S404 of human tau is **phosphorylated** in bovine and porcine tau. **Antibodies** T3P and SMI34 react with **phosphorylated** epitopes that are not unique to PHF-tau and that are not necessarily at the KSPV site.

L2 ANSWER 16 OF 16 MEDLINE
 AN 92302247 MEDLINE
 DN 92302247 PubMed ID: 1376918
 TI Phosphorylation-dependent epitopes of neurofilament antibodies on tau protein and relationship with **Alzheimer** tau.
 AU Lichtenberg-Kraag B; Mandelkow E M; Biernat J; Steiner B; Schroter C; Gustke N; Meyer H E; Mandelkow E
 CS Max-Planck-Unit for Structural Molecular Biology, DESY, Hamburg, Federal Republic of Germany.
 SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Jun 15) 89 (12) 5384-8.
 Journal code: 7505876. ISSN: 0027-8424.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199207
 ED Entered STN: 19920731
 Last Updated on STN: 19980206
 Entered Medline: 19920721
 AB We have studied the phosphorylation of tau protein from **Alzheimer** paired helical filaments, of tau from normal human brain, and of recombinant tau isoforms. As a tool we used monoclonal antibodies against neurofilament protein [Sternberger, N., Sternberger, L. & Ulrich, J. (1985) Proc. Natl. Acad. Sci. USA 82, 4274-4276] that crossreact with tau in a phosphorylation-dependent manner. This allowed us to deduce the state of phosphorylation in normal and pathological tau, as well as antibody epitopes. The epitope of antibody SMI33 is at the first Lys-Ser-Pro sequence motif (residues 234-236) and requires an unphosphorylated Ser-235. Antibody SMI31 binds between Ser-396 (in the second Lys-Ser-Pro motif) and Ser-404, both of which must be phosphorylated. SMI34 has a conformational epitope that depends on the interaction between regions on either side of the microtubule-binding region; it also requires **phosphorylation**. The **phosphorylatable serines** detected by the SMI **antibodies** are part of Ser-Pro motifs and can be **phosphorylated** by a protein kinase activity that can be used to induce a paired helical filament-like state in human brain tau in vitro. The phosphates are incorporated in several stages that can be identified by antibody reactivity and gel shift. This suggests a role for the phosphorylation sites in **Alzheimer** disease, as well as the involvement of a Ser-Pro-directed protein kinase.

L1 ANSWER 25 OF 29 MEDLINE
 AN 95198033 MEDLINE
 DN 95198033 PubMed ID: 7891105
 TI Involvement of tau protein kinase I in paired helical filament-like phosphorylation of the juvenile tau in rat brain.
 AU Takahashi M; Tomizawa K; Ishiguro K; Takamatsu M; Fujita S C; Imahori K
 CS Mitsubishi Kasei Institute of Life Sciences, Tokyo, Japan.
 SO JOURNAL OF NEUROCHEMISTRY, (1995 Apr) 64 (4) 1759-68.
 Journal code: 2985190R. ISSN: 0022-3042.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199504
 ED Entered STN: 19950427
 Last Updated on STN: 19950427
 Entered Medline: 19950418
 AB tau protein kinase I (TPKI) phosphorylates tau and forms paired helical filament epitopes in vitro. We studied temporal expression and histochemical distribution of tau phosphoserine epitopes at sites known to be phosphorylated by TPKI. Antibodies directed against phosphorylated **Ser199** (anti-PS 199) or phosphorylated Ser396 (C5 or anti-PS 396) were used. TPKI is abundantly expressed in the young rat brain and the highly phosphorylated juvenile form of tau occurs in the same period. The activity peak of TPKI coincided with the high level of phosphorylation of **Ser199** and Ser396 in juvenile tau at around postnatal day 8. By immunohistochemistry on the hippocampus and neocortex of 3-11-day-old rats, phosphorylated Ser396 was found in young axonal tracts and neuropil, where TPKI immunoreactivity was also detected. TPKI and phospho-**Ser199** immunoreactivities were also detected in the perikarya of pyramidal neurons. TPKI immunoreactivity had declined to a low level and phosphorylated serine immunoreactivities were undetectable in the sections of adult brain. These findings implicate TPKI in paired helical filament-like phosphorylation of juvenile form of tau in the developing brain.

L1 ANSWER 21 OF 29 MEDLINE
 AN 96034856 MEDLINE
 DN 96034856 PubMed ID: 7566353
 TI Neuronal kinase stimulation leads to aberrant tau phosphorylation and neurotoxicity.
 AU Nuydens R; De Jong M; Nuyens R; Cornelissen F; Geerts H
 CS Department of Cellular Physiology, Janssen Research Foundation, Beerse, Belgium.
 SO NEUROBIOLOGY OF AGING, (1995 May-Jun) 16 (3) 465-75; discussion 475-7.
 Journal code: 8100437. ISSN: 0197-4580.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199511
 ED Entered STN: 19951227
 Last Updated on STN: 19980206
 Entered Medline: 19951107
 AB Neurofibrillary tangles in Alzheimer's disease brain consist mainly of abnormally phosphorylated tau proteins organised in paired helical filaments. Induction of tau phosphorylation in living neurons by hyperstimulation is monitored by specific monoclonal antibodies, such as AT-8 and PHF-1. By quantitative immunocytochemistry, we show that aberrant phosphorylation at the **Ser199**/Ser202 epitope (AT-8) and at the Ser 396 epitope (PHF-1) are moderately induced, proportionally to the degree of kinase stimulation. Whereas AT8 expression is prominent after 48 h, cell death becomes significant at 72 h and is related to the degree of stimulation and the expression level of aberrant tau phosphorylation. Time-lapse videomicroscopy of individual neuroblastoma cells suggest that hyperstimulation leads to a form of morphological over-differentiation. Immediately before cell death, some cells tend to display some features of mitosis. The data suggest a strong correlation between the expression of specific PHF-epitopes and subsequent cell death. The extended time scale of toxicity in this model may be appropriate to study in more detail the steps leading to aberrant phosphorylation associated neurotoxicity.

L1 ANSWER 16 OF 29 MEDLINE
 AN 1998206749 MEDLINE
 DN 98206749 PubMed ID: 9546672
 TI Sequential phosphorylation of Tau by glycogen synthase kinase-3beta and protein kinase A at Thr212 and Ser214 generates the Alzheimer-specific epitope of antibody AT100 and requires a paired-helical-filament-like conformation.
 AU Zheng-Fischhofer Q; Biernat J; Mandelkow E M; Illenberger S; Godemann R; Mandelkow E
 CS Max-Planck-Unit for Structural Molecular Biology, Hamburg, Germany.
 SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1998 Mar 15) 252 (3) 542-52.
 Journal code: 0107600. ISSN: 0014-2956.
 CY GERMANY: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199805
 ED Entered STN: 19980520
 Last Updated on STN: 20021218
 Entered Medline: 19980513
 AB AT100 is a monoclonal antibody highly specific for phosphorylated Tau in Alzheimer paired helical filaments. Here we show that the epitope is generated by a complex sequence of sequential phosphorylation, first of **Ser199**, Ser202 and Thr205 (around the epitope of antibody AT8), next of Thr212 by glycogen synthase kinase (GSK)-3beta (a proline-directed kinase), then of Ser214 by protein kinase A (PKA). Conversely, if Ser214 is phosphorylated first it protects Thr212 and the Ser-Pro motifs around the AT8 site against phosphorylation, and the AT100 epitope is not formed. The generation of the AT100 epitope requires a conformation of tau induced by polyanions such as heparin, RNA or poly(Glu), conditions which also favor the formation of paired helical filaments. The Alzheimer-like phosphorylation can be induced by brain extracts. In the extract, the kinases responsible for generating the AT100 epitope are GSK-3beta and PKA, which can be inhibited by their specific inhibitors LiCl and RII, respectively. A cellular model displaying the reaction with AT100 is presented by Sf9 insect cells transfected with Tau. Knowledge of the events and kinases generating the AT100 epitope in cells might allow us to study the degeneration of the cytoskeleton in Alzheimer's disease.

L1 ANSWER 12 OF 29 MEDLINE
 AN 1999025444 MEDLINE
 DN 99025444 PubMed ID: 9809590
 TI Activation of tau protein kinase I/glycogen synthase kinase-3beta by amyloid beta peptide (25-35) enhances phosphorylation of tau in hippocampal neurons.
 AU Takashima A; Honda T; Yasutake K; Michel G; Murayama O; Murayama M; Ishiguro K; Yamaguchi H
 CS Mitsubishi Kasei Institute of Life Sciences, Tokyo, Japan..
 kenneth@brain.riken.go.jp
 SO NEUROSCIENCE RESEARCH, (1998 Aug) 31 (4) 317-23.
 Journal code: 8500749. ISSN: 0168-0102.
 CY Ireland
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199901
 ED Entered STN: 19990115
 Last Updated on STN: 20021218
 Entered Medline: 19990105
 AB According to the amyloid hypothesis for the pathogenesis of Alzheimer's disease (AD), amyloid beta peptide (Abeta) directly affects neurons, leading to neurodegeneration and tau phosphorylation, followed by the production of paired helical filaments (PHF) in neurofibrillary tangles (NFT). To analyze the relationship between the phosphorylation sites of tau and the activation of kinases in response to Abeta, we treated cultured rat hippocampal neurons with a peptide fragment of Abeta, Abeta(25-35). Abeta(25-35) treatment activated tau protein kinase I/glycogen synthase kinase-3beta (TPKI/GSK-3beta) but not glycogen synthase kinase-3alpha (GSK-3alpha) or mitogen activated protein kinase (MAP kinase) in primary culture of hippocampal neurons. Using antibodies that recognize phosphorylated sites of tau, we showed that tau phosphorylation was enhanced in at least five sites (**Ser199**, Ser202, Ser396, Ser404, and Ser413 numbered according to the human tau isoform containing 441 amino acid residues), to an extent that depended on the level of TPK I/GSK-3beta. Treatment with TPK I/GSK-3beta antisense oligonucleotide inhibited the enhancement of tau phosphorylation induced by Abeta(25-35) exposure. Thus, TPK I/GSK-3beta activation by Abeta(25-35) may lead to extensive tau phosphorylation.